RISK FACTORS ASSOCIATED WITH

LACK OF SEROPROTECTION AGAINST

TYPE 3 POLIOVIRUS

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE MD BRANCH – XV (COMMUNITY MEDICINE) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI, TO BE HELD IN APRIL 2016

Declaration of the Candidate

I hereby declare that this dissertation titled “Risk Factors Associated with Lack of Seroprotection against Type 3 Poliovirus” is a bonafide record of my original research. It has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

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ACRONYMS

BC	Backward Class
BCG	Bacille Calmette Guerin
bOPV	bivalent Oral Poliovirus Vaccinee
CI	Confidence Interval
CNS	Central Nervous System
DPT	Diphtheria Pertussis Tetanus
EPI	Extended Programme for Immunization
EVI	Treatment of enteric infections among Indian infants to improve their response to oral poliovirus vaccine
HAZ	Height for Age Z-score
HBD2	human-beta-defencin2
HiB	HaemophilusInfluenzae B
HIV	Human Immunodeficiency Virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IPV	Inactivated Poliovirus Vaccine
LL37	Cathelicidin antimicrobial peptide
MBC	Most Backward Class
mOPV	monovalent Oral Poliovirus Vaccine
OC	Other Class
OPV	Oral Poliovirus Vaccine
OR	Odds Ratio
P1	Poliovirus Serotype 1
P2	Poliovirus Serotype 2
P3	Poliovirus Serotype 3
RNA	Ribonucleic Acid
SES	Socio Economic Status
SC	Scheduled Caste

tOPV	trivalent Oral Poliovirus Vaccine
VAPP	Vaccine Associated Paralytic Polio
WPV	Wild Poliovirus
SIA	Supplemental Immunization Activities
WHO	World Health Organization
VE	Vaccine Efficacy
VHN	Village Health Nurse
WAZ	Weight for Age Z-score
WHZ	Weight for Height Z-score

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ABSTRACT

Background:

The reasons for lack of seroprotection after Oral Polio Vaccination (OPV) are poorly understood. This study explored socio-demographic, nutritional, birth related, water, sanitation and operational factors to explain lack of seroprotection to type 3 poliovirus, in children 6 - 12 months.

Methods

The study was conducted in Vellore district in rural and urban low income neighbourhoods. This was a case-control study in 142 OPV Type 3 seropositive and 142 seronegative children who had received OPV, selected at random from an existing cohort of children as part of an earlier vaccine study. Data Collection took place between April and May 2015. A questionnaire was administered along with measuring height and weight. Vaccine status was recorded based on vaccination cards where available (83%) and verbal reports from mothers. Univariable and multivariable analysis using logistic regression was done.

Results

The results suggest that some of the explored biological factors, such as feeding colostrums (O.R.:11.77, 95% CI:1.21 – 114.89) and some evidence of early weaning to be associated with vaccine failure. Further, there were trends towards several socio-

economic factors such maternal education (O.R.:0.92, 95% C.I.: 0.86 – 0.99), HAZ score (O.R.:0.82, 95% C.I.:0.65 – 1.04) and being able to name the village health nurse (possibly a proxy for social inclusion and/or education) being associated with vaccine failure (O.R.:1.70, 95% C.I.: 1.00 – 2.88). The per dose vaccine efficacy was calculated to be 26% (7% - 41%).

Conclusion

We identified modifiable risk factors such as early weaning and feeding colostrum. Exclusive breastfeeding should be encouraged as the overall benefit of feeding colostrum with respect to the risk of diarrhea and pneumonia is likely to exceed the risks associated with non-seroconversion to OPV. Other risk factors identified in this study are related to more upstream socio-economic and educational factors tackling of which will require broad political and social measures.

1 INTRODUCTION

Lack of seroconversion following oral polio vaccine is well documented in low income settings across the globe including South Asia. Children living in low income countries and in low income settings within middle income countries have shown to have a lower immune response to oral vaccines as opposed to children from high income settings (1, 2).

Oral poliovirus vaccine (OPV) continues to be the preferred agent over injectable inactivated poliovirus vaccine (IPV) for eradication as the live vaccine produces a local immune response in the mucosal lining of the intestine (the primary site of replication). This in turn prevents the replication and excretion of the virus and places a barrier for its transmission (3). Other reasons include that it is cheap and easier to administer at a larger scale.

Low and middle income countries, including India, are in the process of moving from OPV to IPV. However, until IPV vaccine coverage is greater than 85%, the risk of circulating vaccine-derived polioviruses is high (4). Therefore, OPV continues to be in great demand to prevent this risk till coverage with IPV is adequate. OPV is a crucial part in the end game to the eradication of polio. In this context, the poor response to OPV in low income settings continues to be of high public health relevance.

Many factors have been implicated in its poor immune response, which are yet to be fully understood. With the changing demographics and nutritional transition in low income settings, the need to study these factors is crucial in understanding the best way of using OPV to assist in the eradication of polio.

2. JUSTIFICATION

While several biological and non-biological factors have been implicated in children with vaccine failure, the underlying epidemiological determinants of poor immune response to OPV and other oral vaccines, including cholera and rotavirus, have not been fully understood. In particular, there is a paucity of evidence for the role of socio-demographic, nutritional, gender and operational factors in seroprotection (5).

3. OBJECTIVES

Overall Aim:

To explore risk factors for lack of seroprotection to type 3 oral poliovirus in children between 6 and 12 months of age in rural South India

Specific objectives

1) To assess the effect of socio-demographic, and socio-economic risk factors such as level of education, socio-economic status, water, sanitation and distance to the health clinic on lack of seroprotection to type 3 poliovirus in children between 6 and 12 months.

2) To assess the effect of biological risk factors such as nutritional status, early weaning, feeding colostrum and concurrent illnesses on lack of seroprotection to type 3 poliovirus in children between 6 and 12 months.

3) To measure the per dose protection to type 3 poliovirus in children aged between 6 and 12 months of age immunized with trivalent oral poliovirus vaccine.

4. LITERATURE REVIEW

This literature review consists of two parts. First, an introduction of poliomyelitis, poliovirus and poliovirus vaccination is given. The second part contains focuses on the available literature with respect to evidence for poor immune response to OPV in India and factors influencing this poor immune response.

Polio – historical perspective

It appears that polio infection has for a long time been endemic among human populations. For example, a stone plate discovered from Egypt, depicts a man with a stick as a walking aid. The right leg of this man appears thinned (6). Among medical historians this has generally been interpreted as a sign that this man suffered from polio sequelae (6). Descriptions of cases that might have been due to polio have been reported from ancient

Rome, among them at least one Roman Emperor (5).

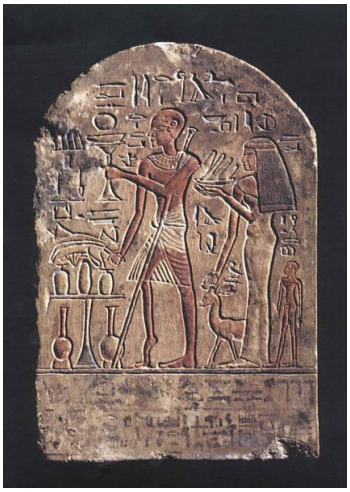


Figure 4.1. Stone plate from Egypt supposedly depicting a man suffering from polio complication

There are no credible reports of polio from ancient Indian sources, but it may be assumed that if polio infection was prevalent in ancient Egypt, then it might also have been present in ancient India.

Perhaps the first person offering a detailed description of symptoms and signs compatible with polio infection might have been proposed by the English doctor Underwood in the late 1700s. An early published report of probable polio infection was given by a German doctor (Jakob Heine) in the mid 1800s, who described Polio infection primarily as a paralysis of the lower extremities (7). A little later, towards the end of the 19th century, a first description of a polio epidemic was made by Karl Oskar Medin, a Swedish doctor of child diseases (7). For some time in Europe, polio infection was even known primarily as Heine-Medin Disease (7).

It is thought that polio infection underwent a change in its epidemiology during the 19th century. Throughout much of human history polio infection may have been largely endemic. Because of the fact that polio infection is asymptomatic or only has minor unspecific symptoms, severe clinical cases might have been perceived as unconnected and sporadic before the 1800s. Reports of outbreaks and large scale epidemics of polio infection only occurred towards the end of the 19th century (6).

Throughout the late 19th and the first half of the 20th century numerous reports from North America and Europe suggested that polio infection had evolved into an epidemic infection, with large scale outbreaks occurring especially in summer months (8). It is not quite clear why this change from endemic to epidemic polio

infection occurred in these areas, and whether similarly, regions outside Europe and North America also experienced epidemics in this time. It has been suggested that socio-economic changes occurring during the industrial revolution in the West may have led to more crowded living conditions and poor sanitation associated with a high exposure to faecal-orally transmitted pathogens such as polio viruses (6). Further, inefficient centralized systems of drinking water provision such as piped distribution systems may have facilitated transmission at large scale (9).

The contrarian view is that it was in fact *improved* sanitation towards the mid 20th century in the West that reduced exposure and consequently immunity to polio in small children who are partially protected by maternal antibodies and in case of infection mostly develop unapparent or mild disease only. This may have meant that the age range of infection was pushed towards older children and adults who are at higher risk of severe disease, thus leading to epidemics of paralytic polio (5, 6, 8).

It was due to the epidemic nature of polio infection in the early 20th century, and perhaps the fact that prominent figures such as President Roosevelt in the US were afflicted by polio infection, that enhanced efforts to develop a potent vaccine against polio were made. Polio affected all population strata, not just poor and disenfranchised people (9).

Polio – pathogenesis and the natural course of infection

Polioviruses belong to the subgroup of enteroviruses within the large family of Picornaviruses, RNA viruses. Enteroviruses such as polioviruses temporarily live in the gastrointestinal tract, and are to survive the acidic environment of the stomach which is a requirement for successful infection of a new host (9). Three distinct poliovirus serotypes are known: P1, P2, and P3. There is little cross-immunity among these three types. Infection and subsequent immunity to one type does not lead to meaningful immunity to the other types (8, 9).

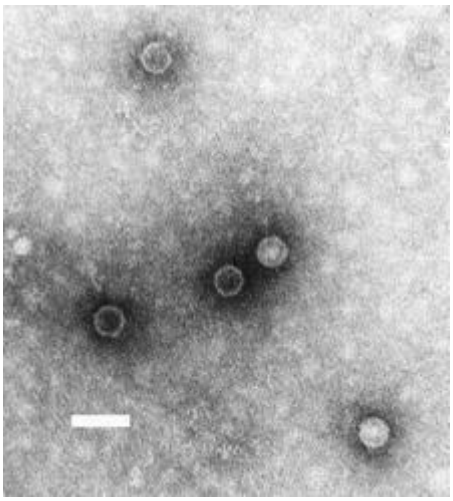


Figure 4.2 Photo of poliovirus under the electron microscope.

Infection with polioviruses occurs through the mouth. The virus then multiplies in the upper respiratory tract and in the gastrointestinal tract, before the onset of symptoms. Polioviruses then enter local lymph nodes and Peyer plaques in the intestines, later going into the bloodstream (8). From here they invade the central nervous system, in particular the motor neurons cells of the anterior horn of the medulla. This then leads to the typical symptoms of flaccid paralysis (8).

The incubation period for polio ranges from just 2 to up to 35 days (9). The incubation period appears to be longer for paralytic polio infection as compared to minor illness (9).

Only about 28% of Polio infection is thought to be associated with disease symptoms (Figure 4.3). Most infected have only few symptoms like fever, generalized fatigue, headache, and gastrointestinal symptoms such as vomiting or diarrhea. Some neck stiffness and myalgia may also occur which may be signs of minor CNS infection and aseptic meningitis (9). Most infected persons recover completely within 14 days. Less than one percent of infected children experience flaccid paralysis, most often in the legs (spinal paralysis) and less commonly of muscles innervated by cranial nerves such as the diaphragm (bulbar paralysis). It has been estimated that about 80% of paralytic polio is spinal only, 2% only in the bulbar region, and perhaps 19% affecting both spine and bulbar region/brainstem (9).

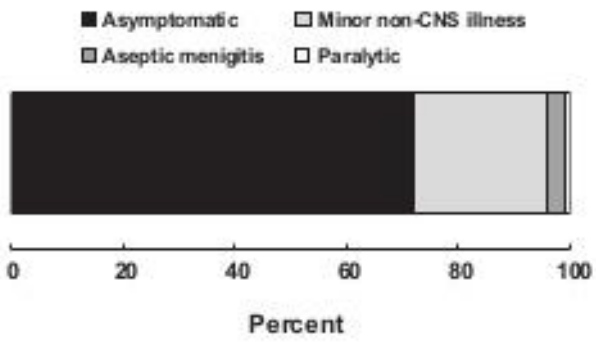


Figure 4.3 Potential outcomes of infection with polio virus.

Bulbar/brain stem involvement may lead to serious disease and death. Overall, between 2 to 5% of children that have developed paralytic polio may die. The figure is higher for adults (15% to 30%). In general mortality is much higher in the presence of bulbar involvement (up to three quarters of cases).

Decades following primary polio infection the so-called post-polio syndrome may occur (10). It is characterized by neurological symptoms such as newly developing weaknesses, atrophy of muscles, dysphagia, dysphonia, or even respiratory failure. Musculoskeletal symptoms such as muscle pain, pain in the joints, or scoliosis may occur. Often, general symptoms such as generalized fatigue and intolerance to cold is experienced by these patients (8).

Transmission

Perhaps the most crucial fact about polio epidemiology is that transmission like that of smallpox is restricted to human beings (6). This makes polio a suitable target for eradication.

Transmission occurs by the faecal-oral route. Hence polio is prone to occur under poor hygienic and sanitary conditions (9). In cold climates polio is occurring particularly during the summer months. In hot climates transmission is more constant throughout the year (9).

Polioviruses are highly communicable. Seroconversion occurs in up to 90% to 100% of susceptible household contacts. Infected persons shed substantial amount

of virus between 8 to 10 days before beginning of symptoms and for a similar period afterwards. Shedding may continue for up to 3 to 6 weeks after onset of symptoms (11).

While infected persons shed large amounts of virus through their faeces, immune competent persons completely eliminate the virus after a few weeks. This means there are no chronic asymptomatic carriers of polio viruses in healthy individuals. However, in immune deficient people such as HIV infection, polio viruses may not be cleared from the body and viral shedding may continue chronically (11). This may have important implications for the post-eradication/post-elimination phase as immune-compromised individuals may represent an ongoing reservoir, which highlights the importance of keeping up vaccination in the population for a long time after eradication (12).

Vaccination against Polio

There are two classes of polio vaccine for use in the general public. 1) Inactivated poliovirus vaccine (IPV), an inactivated injectable vaccine, and OPV, a vaccine formula that contains attenuated live polio viruses. These live viruses can revert to a virulent form (Figure 4.4), causing vaccine-associated paralytic polio (VAPP) (3).

Oral polio vaccine is a combination of three live attenuated poliovirus serotypes (Sabin types 1, 2 and 3) and was introduced in 1961(9). OPV was first developed as monovalent formulations against the three serotypes separately and used from the early 60s, and later from the mid 60s as a trivalent vaccine. OPV replaced IPV

as it is cheaper, can be given orally and may induce a longer lasting immunity (13). Since polio serotype 2 appears to be no longer circulating worldwide and type 2 is associated with VAPP, the trivalent OPV is being replaced by bivalent OPV that no longer contains serotype 2 (3). A rare but serious adverse effect of OPV is vaccine-associated paralytic poliomyelitis(VAPP), which is clinically similar to polio caused by wild poliovirus(WPV), with features of neurovirulence (14).

OPV viruses are found in the stool for up to 6 weeks after vaccination. Most of the virus shedding happens in the first 2 weeks post-vaccination. Vaccine viruses are able to spread to close contacts of vaccine recipients when they come into contact with faecal material containing the vaccine virus. These contacts may even develop VAPP if they themselves are not vaccinated (3).

Inactivated Poliovirus Vaccine was in use in the US and other countries from 1955(3). Scandinavia and Netherlands have, with IPV alone, managed to eradicate polio(9). IPV was largely replaced by OPV from the 1960s. Post-elimination its use became the vaccine of choice in the US and in many European countries, as it does not cause VAPP. IPV is made from inactivated (killed with formalin) wild-type poliovirus strains of each serotype. Current IPVs are delivered either as stand-alone trivalent vaccine or as part of a combination vaccine alongside DPT (diphtheria, pertussis and tetanus) with or without *Haemophilus Influenzae* B (HiB) or Hepatitis B(15).

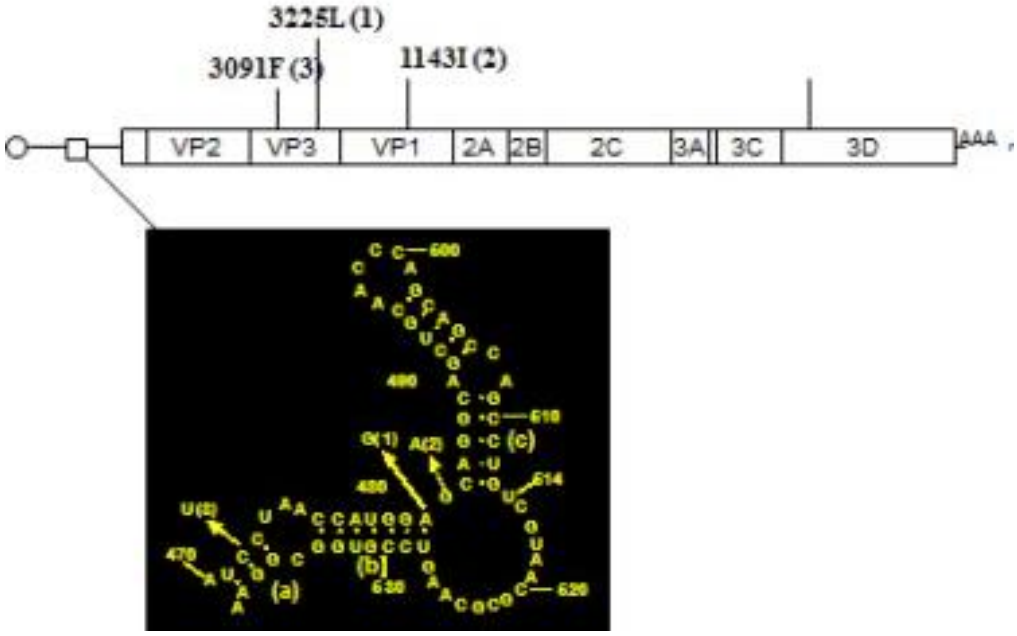


Figure 4.4 Schematic diagram of the poliovirus showing possible mutations in OPV strains that may cause reversal to a neuropathogenic strain. Vaccine derived polioviruses have mutations in the V Domain of a non-coding region. They also have at least one mutation in the capsid region at the other end. The polio types are marked in parenthesis. From Minor(15)

Although IPV does not induce mucosal immunity, it has the advantage of not causing live-virus-associated risks such as VAPP and has very transient and minimal adverse effects (3). Disadvantages of IPV use include the inconvenience of an injectable vaccine and the need for skilled personnel to deliver injectable vaccines. The other disadvantage is the need for containment of manufacturing areas in view of risks associated with WPV, which is needed to produce IPV. Attenuated Sabin strains are in turn being developed to prevent retransmission in a post-elimination era (16).

Table 4.1 Immunisation schedule in India

VACCINE	INFANTS	CHILDREN
BCG	Birth/ as early till 1 yr	
HEPATITIS B 1,2,3	Birth/ as early till 24 hrs; 6,10,14 wks	
OPV 0 1,2,3,4	Birth/ as early till 15dys; 6,10,14 wks	
DPT 1,2,3,Booster	6,10,14 wks;	16-24 months
MEASLES 1,2	9 months (completed) – 12 mo	16-24 months
VITAMIN A	9 months	Every 6 months (2^{nd}– 9^{th} dose)
JAPANESE ENCEPHALITIS		16-24 months
TT		10yrs & 16yrs

The current Government of India vaccine schedule (Table 4.1) prescribes 5 doses of OPV for children in the country: at birth, at 6, 10 and 14 weeks, and one booster in 16 to 24 month-old children.

Elimination of Polio in India

Until quite recently there was a lot of skepticism as to the potential for eliminating polio infection in India (17). As late as 2004 some critics called a polio-free India a "distant dream" (16, 18-20). Reasons for skepticism were partly operational and partly based on immunological grounds (16, 17). The latter reason is related to the topic of this thesis, i.e. the finding that in low income settings, many children remain susceptible to polio even after administering many doses of OPV (21).

Nevertheless, India was declared as no longer endemic for polio in 2012 (22). India was declared polio-free in early 2014, after having experienced no case of polio for three consecutive years (22). Milestones in the elimination-drive of polio in India are given in Table 4.2.

Table 4.2 Milestones in the elimination of polio in India.

1988	Target for polio eradication by 2000 set by World Health Assembly (WHA)
1993/1994	Tamil Nadu and Kerala States - special drives conducted to administer polio vaccines.
1994	Delhi State conduct 2 Polio vaccination drives.
1995/96	National Days (NIDs) - polio vaccination, 2 conducted.
1996	Vaccine Vial Monitor used
1997	National Polio Surveillance Project set up as WHO and Govt of India collaboration.
1999	Last case of wild polio virus type 2 (WPV2) - Aligarh, U.P.
1999	Polio drive: changed booth activity to house to house coverage.
2002	Social Mobilization Network - set up for community mobilization.
2005	Monovalent oral polio vaccine (mOPV) used
2010	Bivalent oral polio vaccine (bOPV) used for polio campaigns in India.
Nov 2010	Last reported wild polio virus in sewage sample - Mumbai, India
22 Oct 2010	Last case of wild polio virus type 3 (P3) -Pakur, Jharkhand.
13 Jan 2011	Last case of any type of wild polio virus (P1) - Howrah, West Bengal
25 Feb 2012	India no longer polio endemic country (removed WHO list)

Polio vaccination using OPV was done in Mumbai from 1964 and in Vellore from 1965. Systematic vaccination with OPV started in the late 1970s under the Extended Programme for Immunisation (EPI) scheme (23). As can be seen in Figure 4.5, the number of polio infections declined continuously from the late 80s. The decline went in parallel with that of other vaccine preventable conditions (24).

Elimination of polio in India required an intense, well-planned and coordinated effort to be sustained for years and there were many setbacks (24). Enhanced efforts, also known as Supplemental Immunization Activities (SIA) to eliminate polio were made from 1995 (21). This included National Immunization Days and large-scale additional campaigns in endemic areas of India such as UP and Bihar, where vaccine coverage was traditionally low (21). Estimated 2.3 million field staffs were employed from the year 2000 to vaccinate millions of children. Particular efforts were made to reach pastoral populations and migrants, including children of migrant workers travelling for example by train (23).

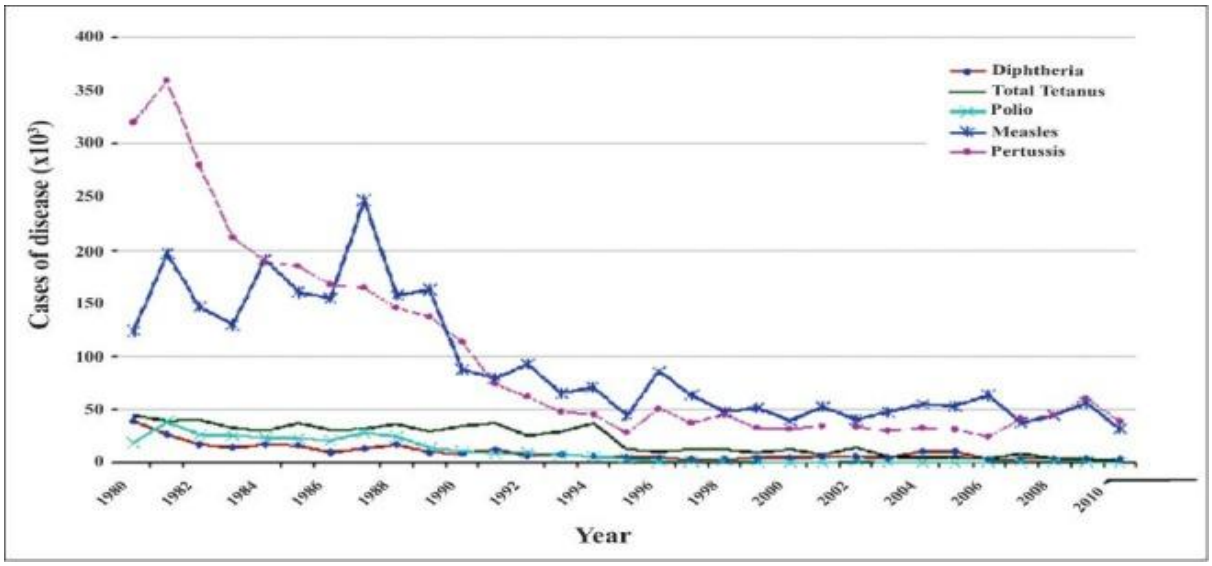


Figure 4.5 Trends in case numbers of polio and other vaccine preventable conditions. From (21)

For much of the campaigns from 2005, monovalent OPV (type 1 and type 3) was used, as these were more effective than the trivalent OPV (21). However, under-use of OPV type 3 left children susceptible to type 3 (Figure 4.6). Hence, from 2010, in the final drive for elimination, bivalent OPV containing type 1 and 3 were introduced (8).

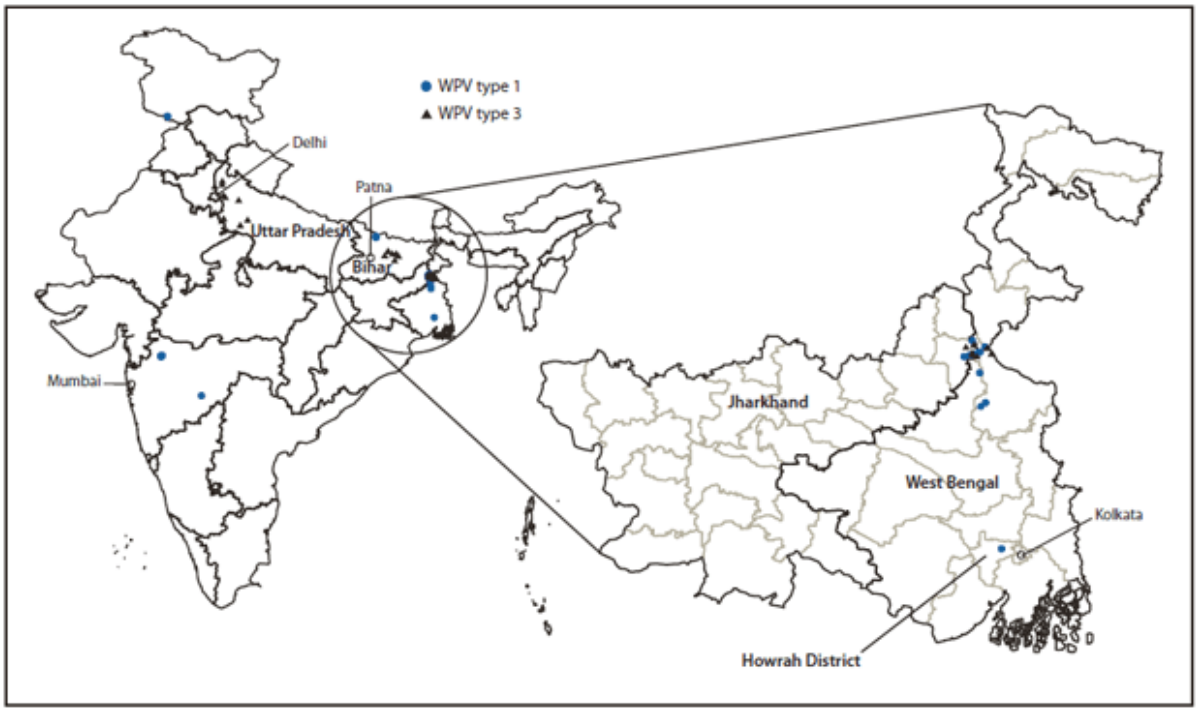


Figure 4.6 Cases of polio wild types type 1 and type 3 during 2010 and 2011.

India is close to countries that still report polio cases and that, mainly for political reasons and internal unrest may remain polio-endemic for some time, namely Pakistan and Afghanistan (Figure 4.7). India thus remains at high risk for re-introduction of wild poliovirus (WPV) (8). Because of this fact, maintaining a high immunity against polio infection at population level is of utmost importance and the topic of this thesis. Efforts to maintain high immunity are outlined in the next section.

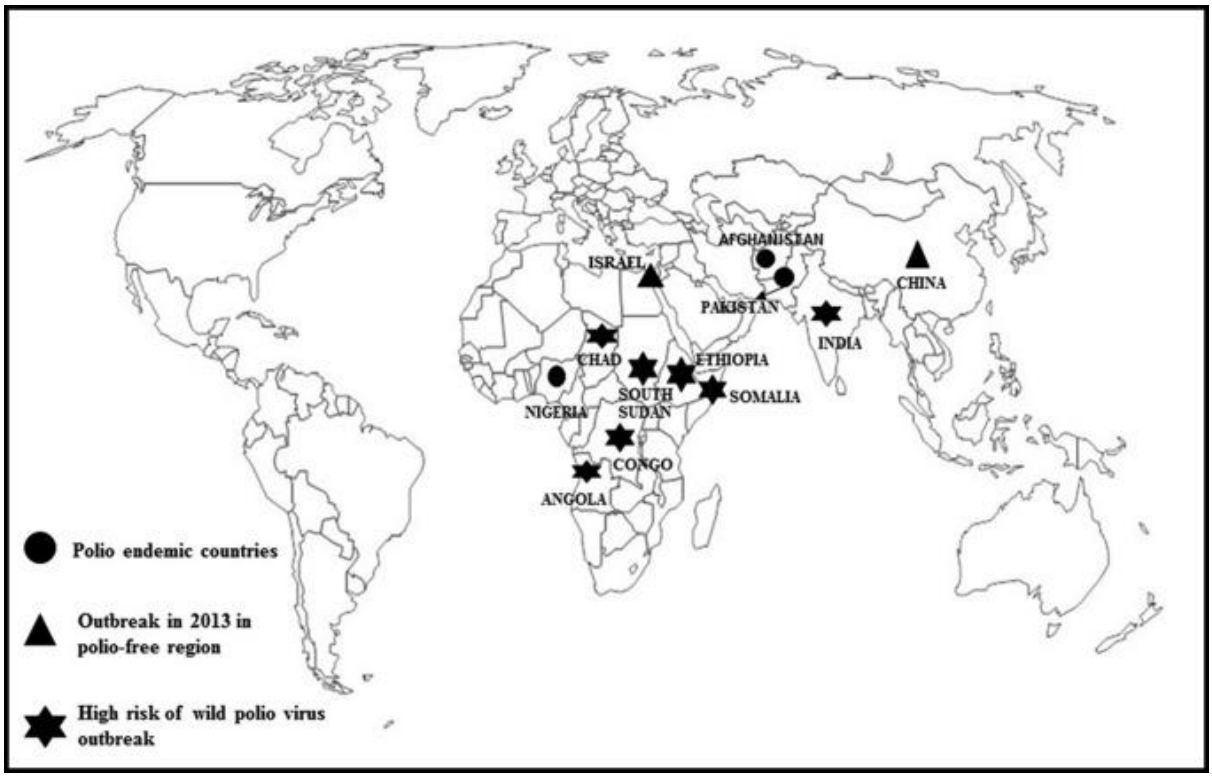


Figure 4.7 Polio endemic countries and countries at high risk of wild-polio virus outbreaks.

Maintaining immunity at population level in the post-elimination phase

Several factors specific to polio and polio vaccination explain why it is crucial that, after elimination of polio in India and even after global eradication, a high level of immunity against polio virus at population level will be required for many years.

First, polio viruses including vaccine derived polio viruses exhibit a certain amount of environmental stability (25), although they are inactivated by sunlight and high temperatures (11). More importantly, the continuing possibility of conversion of attenuated polio viruses used for vaccination to more virulent forms means potential

exposure to susceptible individuals as long as OPVs are in use. It has further been shown that immune-compromised individuals can serve as a long term reservoir for polioviruses, either vaccine-derived or wild types (24).

Increased international travel means that polio viruses endemic in one country may quickly be introduced into other countries that are free of polio transmission. Several outbreaks of polio have occurred in this fashion (Figure 4.7) (24). During the past ten years, 40 countries experienced outbreaks of poliomyelitis following importation from polio-endemic countries (26, 27).

In 2013, an outbreak occurred among children in Somalia, which had been free of polio since 2007(28). The outbreak also led to cases of polio in neighbouring Kenya which had also been free of polio for several years. Wild type poliovirus was detected in sewage samples across a multitude of environmental sampling sites in Israel in 2013. The virus was identified to have originated from Pakistan and introduced into Israel via Egypt. Although no cases of flaccid paralysis have occurred in Israel since detection of poliovirus, this case highlights the potential for the virus to cross international borders quickly and insidiously (29).

A detailed report about an outbreak of polio in Xinjiang province in China where about 50 cases of polio infection were identified by public health authorities (30). Again the virus appears to have originated from Pakistan. The authorities responded with a large scale containment effort that included 5 rounds of vaccination with monovalent and trivalent OPV, alongside enhanced surveillance. The costs for

containing the outbreak were about 25 million USD highlighting the immense logistics and costs involved in responding to outbreaks(24).

If a high level of immunity needs to be maintained for some time to reduce the risk of re-introduction of wild type poliovirus the question arises as to what vaccine should be used to achieve this. OPV is associated with the risk of developing vaccine derived polioviruses and VAPP. Hence OPV cannot eradicate polio on a global scale. As long as children are vaccinated with OPV the risk of polio will remain (13). Hence the shift from OPV to IPV is seen as mandatory to achieve true eradication. A phased approach is likely to take place in the majority of countries that are still using OPV(13). In the long run, to fully eradicate polio, only IPV may need to be used, as is already the case in many high income countries, where the higher costs of IPV are not an issue.

WHO has developed the Polio Eradication & Endgame Strategic Plan 2013-2018 outlining the rationale behind switching from trivalent OPV to bivalent OPV, which leaves children susceptible to type 2 (both wild type and vaccine derived). To prevent this, it is recommended to add one dose of IPV to the schedules, which contains antigens of all three polio serotypes thereby protecting against type two after switching to bivalent OPV (31, 32). IPV has been shown to boost mucosal immunity to polio after OPV (33).

A range of operational issues in vaccine delivery has been noted that need to be consistently tackled to maintain a high immune status in the population. In a recent study looking at immunization coverage in an urban population in Tamil

Nadu, routine immunization coverage was found to be 81% (34), indicating possible gaps in operational systems in providing adequate doses of polio. New initiatives are being evaluated, such as mobilizing existing community health worker structures (2).

Evidence and risk factors for the poor immunity to polio after OPV in low income settings

The search was done in PubMed without restriction to year of publication. The search was conducted up to August 10th 2015 Articles published beyond this date were therefore disregarded. Papers were restricted to the English language. Papers were eligible if they contained original field research or were review articles thereof. Reference lists of identified articles were searched for further articles for inclusion. The following key words were used for the search in this section: [polio* OR OPV] AND "Vaccine efficacy" AND [India OR Africa]; [polio* OR OPV] AND immun*; [polio* OR OPV] AND mucosa*; [polio* OR OPV] AND diarrh*; [polio* OR OPV] AND enterovir*; [polio* OR OPV] AND malnutrition; [polio* OR OPV] AND enteropathy.

Issues with reduced VE in low income settings were first reported in India including Vellore. An early study of poor response to OPV was published by John and colleagues (2). This study clearly found that immunogenicity to OPV is much lower in India than could be expected based on data from high income countries. The was study done, in children aged 3 months and 6 years, in Vellore, Tamil Nadu. In 191 children before a first dose of OPV, 28%, 7% and 6% of children

were already seropositive to types 1, 2 and 3, respectively. Among the seronegatives, trivalent OPV produced seroconversion in 35% to type 1, 75% to type 2 and about 50% to type 3 after having received 2 doses 2 months apart (35). The clinical relevance of this poor vaccine response could be demonstrated in further studies showing that poliomyelitis occurs regularly in children who previously received OPV (36).

A study from Delhi demonstrated seroconversion after three doses of trivalent OPV in children of about 65%, 80% and 60% to polio types 1, 2 and 3 respectively (37). The study further showed that increasing the vaccine dose given at each vaccination does not influence seroconversion. Similar figures were found in an earlier study from Delhi published by Ghosh et al (38). A study from Mumbai published in 1977 by Pangi et al showed an equally poor response to oral polio vaccine (39).

A study from Nigeria estimated vaccine efficacies per dose of monovalent type 1 OPV and trivalent OPV against paralytic poliomyelitis (type 1) to be 67% and 16% (95% CI, 10 to 21), respectively (40). This highlights the poor efficacy especially of the trivalent vaccine, probably due to interference among the vaccine strains (39). The estimated efficacy of trivalent oral poliovirus vaccine per dose against type 3 paralytic poliomyelitis was also very low at 18% (41). A second study from Nigeria found an effectiveness against vaccine derived polio virus infection to be 38% of the trivalent OPV, which was higher than the efficacy found against wild-type poliovirus type 1 (13%) and type 3 (20%). Similar to the

above studies in India, the study found that frequent repetition of vaccination substantially improves efficacy (42).

A study in Uttar Pradesh found that in places with ongoing poliovirus transmission, the protective efficacy of monovalent OPV against type 1 was about 30% per dose compared with 11% for the trivalent OPV (43). A randomised controlled trial in India found that bivalent OPV (types 1 and 3) was again far more efficacious than trivalent OPV, and resulted in a comparable immune response compared to the monovalent OPV against type 1 and type 3 given separately (40, 44).

Risk Factors for Poor immune response to OPV

Many factors have been studied that may influence immune response following OPV in children in low income settings(45). The lower immunogenicity, in both humoral and mucosal immunity, in India and other countries, where a substantial proportion of the population live in low income settings, calls for further research into risk factors associated with non-seroconversion (46-50). The main factors that have been studied are listed below (Table 4.3):

Table 4.3 Overview of potential risk factors for a reduced immune response against oral poliovirus vaccine.

Maternal factors		References
	Breastfeeding	(48, 51, 52)
	Maternal antibodies	(48, 53, 54)
Childhood infections		
	Diarrhea	(2, 46, 50, 55, 56)
	Non-polio enterovirus co- infection	(57)
Child nutritional factors		
	Malnutrition	(54, 58-61)
	Environmental enteropathy (Tropical Enteropathy)	(62, 63)
Child demographic factors		
	Age	(64)
	Gender	(50, 52).

Breastfeeding and maternal antibodies

There is a debate with regard to the effect of exclusive breastfeeding on immune response to OPV. A study conducted in India and published in 1980 suggested that exclusive breastfeeding may reduce immune response to polio types 1, 2 and 3 by 33%, 17% and 12% respectively (49). The mechanism may be maternal antibodies. Similarly, an earlier US study found that breastfeeding may reduce vaccine immune response by about 25% (48). A study conducted in Brazil suggested that high levels of maternal antibodies to the three poliovirus types led to a higher chance of vaccine failure (48). In this study, breastfeeding was

associated with a marginal reduction in immunogenicity to poliovirus types 1 and 2 and a more marked reduction (of 30%) to type 3 (54). A study done at Dhaka evaluating reasons for failure to mount an immune response to OPV found a short duration of breastfeeding to be a significant risk factor. Each additional month of exclusive breastfeeding increased OPV titres (46).

By contrast, a study in Uganda comparing breastfed and formula fed children found no evidence for a reduction in the immune response to monovalent OPV type 1, and if anything even an increase in immunogenicity by about 20% (47). Similarly, a study in Tunisia estimated a similar increase in immunogenicity (52). However, the last two studies were fairly small, with wide confidence intervals that make it difficult to interpret the findings. However, another study also supported this finding with higher anti-polio IgA responses in those who were exclusively breastfed (51). A trial in Egypt found that high maternal antibodies clearly reduced immune response to OPV in newborns. However, this study also found that in children with high maternal antibodies to polio, monovalent OPV was much more effective in achieving seroconversion than trivalent OPV (46% versus 21%) (40). Overall, the effect of breastfeeding on immunogenicity of OPV appears to be small, especially when monovalent OPV is used.

Diarrhoea

It is biologically plausible that diarrhoeal disease episodes concurrent or preceding OPV may affect the efficacy of vaccination. The mechanism may be that gut clearing of OPV viruses may be enhanced during diarrhoea as stool passage time

is reduced. Further, non specific immune responses (e.g. by cytokines or complement factors) that is elicited by concurrent gastrointestinal infection may suppress the OPV polio vaccine strains in a way that prevents or lowers the stimulation of specific antibody production (48). However, evidence appears conflicting.

A study from Gambia found some evidence that diarrhoea reduced the immunogenicity to type 3 poliovirus by about 15% while seroconversion to type 1 and 2 were hardly affected (48). Similarly, a study from Brazil conducted jointly with the Gambia study suggested that seroconversion to type 3 poliovirus is reduced by 18%. Immune response to type 2 was reduced by 7% whereas immune response to type 1 was not affected (53). A study from Bangladesh conducted in 1996 among 6 to 16 weeks old children found that seroconversion after the first dose of trivalent OPV was reduced in the presence of concurrent diarrhoea by 34% with regard to type 3 and 26% with regard to type 2 poliovirus. Again there was no effect on type 1 poliovirus immune response (53). Seroconversion was however hardly impaired in children with diarrhoea who received the third dose of trivalent OPV (54).

The already above mentioned study done at Dhaka evaluating reasons for failure to mount an immune response to OPV also found diarrhea to be a significant risk factor (65). Children with two or more episodes of gastrointestinal infection during the first months after birth had more than twice as high a risk to fail to mount an adequate immune response to OPV as those who had only one episode or no episode at all ($p=0.02$).

A study from Brazil found that diarrhoea reduced seroconversion to type 1 (-14%), type 2 (-64%) but not to type 3 after the second dose of OPV. There were only small and inconsistent effects of diarrhoea on immune response to the third or fourth dose of OPV (59). A serosurvey conducted in Pakistan found that diarrhoea in the past six months to be associated with lack of seroconversion after OPV (40).

On the whole the results suggest that diarrhoea may considerably reduce the chances of seroconversion after the first and second doses of OPV, but that the efficacy of subsequent doses to elicit an adequate immune response is hardly impaired.

The effect of concurrent infection with enteroviruses other than polio

Concurrent infection with enteroviruses other than poliovirus has been proposed as a possible factor that may reduce immune response to oral poliovirus vaccines. Similar to other gastrointestinal infections, these enteroviruses may cause a non-specific immune reaction that may suppress poliovirus vaccine strains. In addition to other gastro-intestinal pathogens, enteroviruses other than polio may due to phylogenetic closeness to polioviruses also cause a specific antibody response leading to the shedding of antibodies that may cross-react with OPV antigen (2).

A number of studies have been conducted to examine this question. An early study conducted by John and Jayabal in Vellore exploring the effect of concurrent enterovirus infection on shedding of polio vaccine viruses post OPV found no

evidence that enterovirus infection impaired infection with the vaccine strains. Seroconversion however was not measured in this study (55).

In a study from Mexico on rural Mayan children (a poor setting) found that concurrent enterovirus infection reduced immune response to OPV by as much as 43% (50). A study from India published by Idris and colleagues found that enterovirus infection reduced seroconversion to OPV by about 15% for all three vaccine strains (56). Similar observations were made by Swartz and colleagues in Israel who found non-polio enteroviruses to reduce seroconversion following OPV by up to 47% (type 1), 17% (type 2) and 29% (type 3) (56). However, their results were not consistent and were restricted to one season, while in a previous season, hardly any impact of enteroviruses were found. Seasonal changes in enterovirus force of infection may explain these conflicting trends (46).

Domok and colleagues found in a study in Uganda that non-polio enteroviruses interact with monovalent type 1 OPV and reduce seroconversion by 24%. Of 38 children with concurrent enterovirus infection 45% seroconverted, whereas in the 49 children without concurrent enterovirus infection 59% seroconverted. However, statistical support for this finding was low ($p= 0.2$). The authors also report that repeated vaccination with OPV can markedly reduce the deleterious effects of enterovirus co-infection (47).

Triki and colleagues found in their small sample of 121 Tunisian children that coinfection with non-polio enteroviruses was prevalent in 50% of children that failed to mount an adequate immune response. By contrast, none of the children

with an adequate immune response was found to be positive for non-polio enterovirus infection (66).

Malnutrition

It has been generally suggested that malnutrition plays a minor role in reducing seroconversion to OPV and other vaccines (54). The literature on OPV provides with mixed results. In the study from Dhaka in Bangladesh mentioned above, malnourished children (Weight for age z score <-2) had markedly lower OPV 3 titers (difference in medians 0.9, p=0.03) than children without signs of malnutrition (58). In multivariable quantile regression analysis, compared with malnourished children, normal children had 2.35 (95% CI: 0.66–4.03, p = 0.0065) and 1.11 (95% CI: 0.31–1.90, p = 0.0063) higher OPV titer 3 measures at the 25th and 50th percentiles of OPV response, respectively.

In a study conducted in north India to assess seroprevalence of antibodies to different types of poliovirus, malnutrition was found to be associated with a lower seroprevalence of antibodies to type 3 (59). In a study from Pakistan stunting was clearly found to be associated with failure to seroconvert (57). Similarly, a serosurvey from Pakistan in children with at least 7 documented doses of OPV, protein-energy malnutrition was strongly associated with lack of seroconversion (60).

A randomized controlled trial in Pakistan also found that severely malnourished children were at high risk of failure to seroconvert after bivalent OPV alone (67,

68). Interestingly, this trial found that combining OPV and IPV in these children led to an immune response comparable to children that were not malnourished.

Environmental Enteropathy

Studies in malnourished children and adults temporarily living under poor hygienic conditions have suggested a direct link between exposure to poor hygiene and chronic inflammatory changes in the intestines that are characterized by a decrease in the villous height, infiltration of inflammatory cells, increased intestinal permeability (results in the impairment of the gut's barrier function against unwanted products), and a worsening of the intestinal absorption of essential nutrients (67, 68). This chronic condition is known as tropical or environmental enteropathy (67, 68).

Evidence that environmental enteropathy may play an important role in the development of undernutrition in low-income settings is mounting (69, 70). Studies in the Gambia have suggested that environmental enteropathy may explain about half of the growth faltering in infants (61).

There is also some evidence that environmental enteropathy may impair immune response to oral poliovirus vaccine. A study from Bangladesh found that in children with abundant *Bifidobacterium infantum* colonization in their guts, immune response to polio and BCG vaccination (measured as the specific T cell response) was higher than in children with reduced *Bifidobacterium infantum*

predominance, which is a feature of environmental enteropathy. The authors speculated that vaccine effectiveness may be enhanced by promoting the intestinal symbiotic flora (62). An experimental study conducted in health adult volunteers found that probiotics enhance immune response, by increased poliovirus neutralizing antibodies, which again enhanced the shedding of poliovirus-specific IgA and IgG in serum (71).

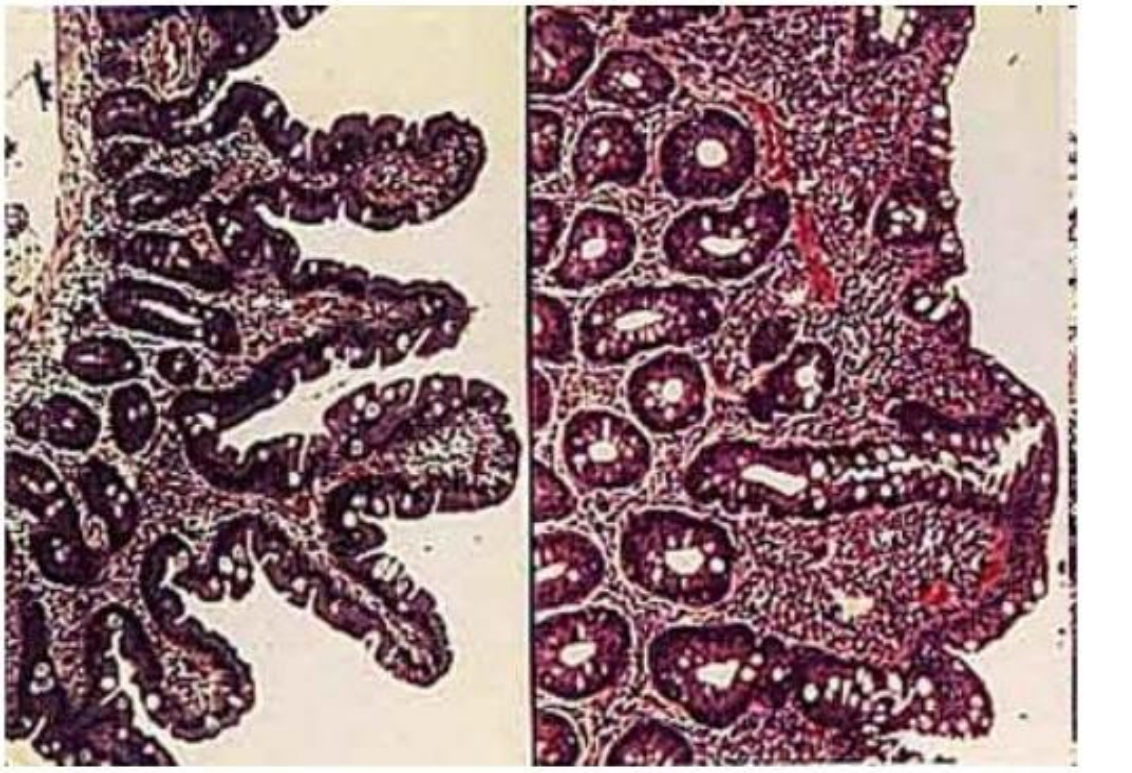


Figure 4.8 Environmental Enteropathy

On the whole these studies suggest that environmental enteropathy may be an important factor in limiting seroconversion in children in poor and unhygienic settings (63), but more studies are clearly needed to confirm this suspicion.

Age, socio-demographic and geographic factors

Studies done in low socioeconomic settings in Pakistan found age, total and campaign OPV doses to be associated with higher seroprevalence. Seroconversion rates at birth were found to be low to poliovirus type 1 after mOPV1 or tOPV given at birth but high for all formulations of mOPV1 given at age 30 days, with a possible explanation linked to the presence of maternal antibodies (72). However, a large variability exists in seroconversion rates at birth, which is not completely understood (73).

In India, variations in mucosal immunity was also noted to differ with location, serotype and vaccine formulation (48, 74), with the immunogenicity of OPV also appearing to vary with the season (64).

Gender

The effect of gender on seroprotection to poliovirus following vaccination is unclear. In a seroprevalence study conducted in Nigeria, number of OPV doses, maternal education and gender were associated with seroconversion (52).

A recent study has revealed one dose of OPV and BCG to be associated with higher excretion of gut cathelicidin (LL37) in infants at 6 week of age. Girl infants were found to have higher human-beta-defencin2 as compared to boys

(HBD2) (75). HBD2 is a member of the defensin family of antimicrobial peptides that plays important roles in the innate and adaptive immune system (76). LL37 plays a similar role (77).

Several studies with other vaccines have shown differences in gender. One study found females had higher neutralizing antibody titers following smallpox vaccines than males (78-83). Sex-differential adverse effects have also been noted in vitamin A supplementation, DPT, measles vaccine and anthrax vaccine (84, 85).

Non-specific effects of vaccination have been noted to vary in gender in a twin pair study (86). Women have also had more reactions to adsorbed anthrax vaccine as compared to men (87) and had higher titres to measles vaccines (88).

In summary, the literature review suggests that coinfection with enteroviruses other than polio may be the strongest measureable factor associated with failure to seroconvert that has been studied so far. However, it also seems that repeated doses of OPV can overcome this problem.

The effect of malnutrition on OPV efficacy is not well understood. Currently available studies however, appear to exclude large effects, but more research is needed to confirm this. Environmental enteropathy has not been well studied as a risk factor for failure to seroconvert following OPV. More research is needed in this emerging field of research.

The risk factors for failure to be seroprotected following immunization are equivocal and to our knowledge not well established. Our intent is to evaluate a

few risk factors including protein energy malnutrition, operational and socio - demographic factors. We are unaware of literature from this region or from the rest of India that have evaluated these factors in the past 20 years. The demographic and nutritional transition that the population has undergone and increasingly conflicting evidence on the role of malnutrition and gender on immune responses to vaccine makes us believe it is particularly relevant that these factors be evaluated afresh.

5. METHODOLOGY

Study Setting

The study was conducted in Vellore district in the southern Indian state of Tamil Nadu. Three blocks were chosen for the study based on the fact that an ongoing OPV surveillance system in the context of an ongoing clinical study (EVI trial, http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=9069) in these areas offered the chance to easily obtain a sampling frame for the study. The areas included in the study were Vellore Town, as well as Kaniyambadi and Anaicut Blocks. The study area in Vellore Town included a mix of predominantly urban neighbourhoods some of which consisted of formal settlements while others resembled unplanned urban slums. Low income neighbourhoods predominated in the OPV surveillance sample used as a sampling frame, and was not a representative sample of the whole of Vellore town. Kanyiambadi and Anaicut blocks are mainly rural where agriculture predominates around smaller sized towns. The furthest distance travelled was to Pallikonda in the Anaicut block, which was approximately 23 km away. Recruitment and data collection took place between April and May 2015.

Study Design

This study was performed as a case control study on seropositive and seronegative children previously identified during screening for recruitment of seronegative children to the EVI trial. Children between 6 and 18 months are considered to

have the highest risk of neuroparalytic poliomyelitis and ascertaining protection in this age is important.

Selection of Cases and Controls

Cases definition: All children between the ages 6 – 12 months in the Vellore and Kaniyambadi block who were recruited as part of the EVI study and were found to have antibody titres less than 1:8 dilution to type 3 OPV.

Exclusion criteria: Child who received Inactivated Polio Vaccine prior to blood sampling for the EVI study.

Control definition: Children between 6-12 months from the same study area with serum neutralizing antibody titres greater than or equal to 1:8 dilution against type 3 OPV.

As part of screening for eligibility in a large pragmatic clinical trial (EVI study) that included seronegative infants between 6 and 12 months of age, 8454 infants were tested for neutralizing antibodies to type 3 poliovirus. A total of 284 children were selected by an independent statistician without details of the antibody test. This 284 children included a random subset of 142 seronegative children designated as "cases" and 142 seropositive children designated as "controls", whose status were unmasked only after all data was gathered by the investigator.

Cases and controls were visited at home and the primary caregiver, following informed consent, was administered a structured questionnaire on details nutritional anthropometry at home. Although the age group was 6-12 months for

the clinical trial, there was an average of 6 months from that point to when this case control study was done.

Sample Size

For the sample size calculation the study was treated as an unmatched case control study with 1 control per case, ignoring the stratified matching approach based on location. We calculated the sample size to estimate the association of malnutrition with failure to be seroprotected. National Family Health Survey -3 indicates underweight for age to be 40.2% in children 12-17 months. Since seronegative status is sufficiently rare, we assumed this to be the prevalence of malnutrition in the control population. If the true odds ratio for seronegative status in malnourished subjects relative to well-nourished subjects is 2, we would need to study 134 case patients and 134 control participants to be able to reject the null hypothesis that this odds ratio equals 1 with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We used a Fisher's exact test to evaluate this null hypothesis.

An odds ratio of 2 was assumed resulting in an expected prevalence of exposure among the cases of p1= 0.573.

The sample size was calculated using the following formulae:

$$\mathrm{n} = \frac{r+1}{r} \times \frac{(p)(1-p)(Z\propto_{/2}+Z_{\beta})^2}{(P_{1-}P_2)^2}$$

Assuming 80% power and alpha= 0.05, and a ratio of cases to controls of 1:1 results in 134 cases and 134 controls.

(P1) =P0*OR/(1+P0(OR-1))=0.573

$\bar{P}$= (P1+P0)/2= (0.402+0.573)/2=0.4875

$\bar{Q}$= (100- $\bar{P}$) =0.5125

d= P0-P1=0.171

n= (Zα +Zβ)²*$\bar{P}$*$\bar{Q}$*2/d²

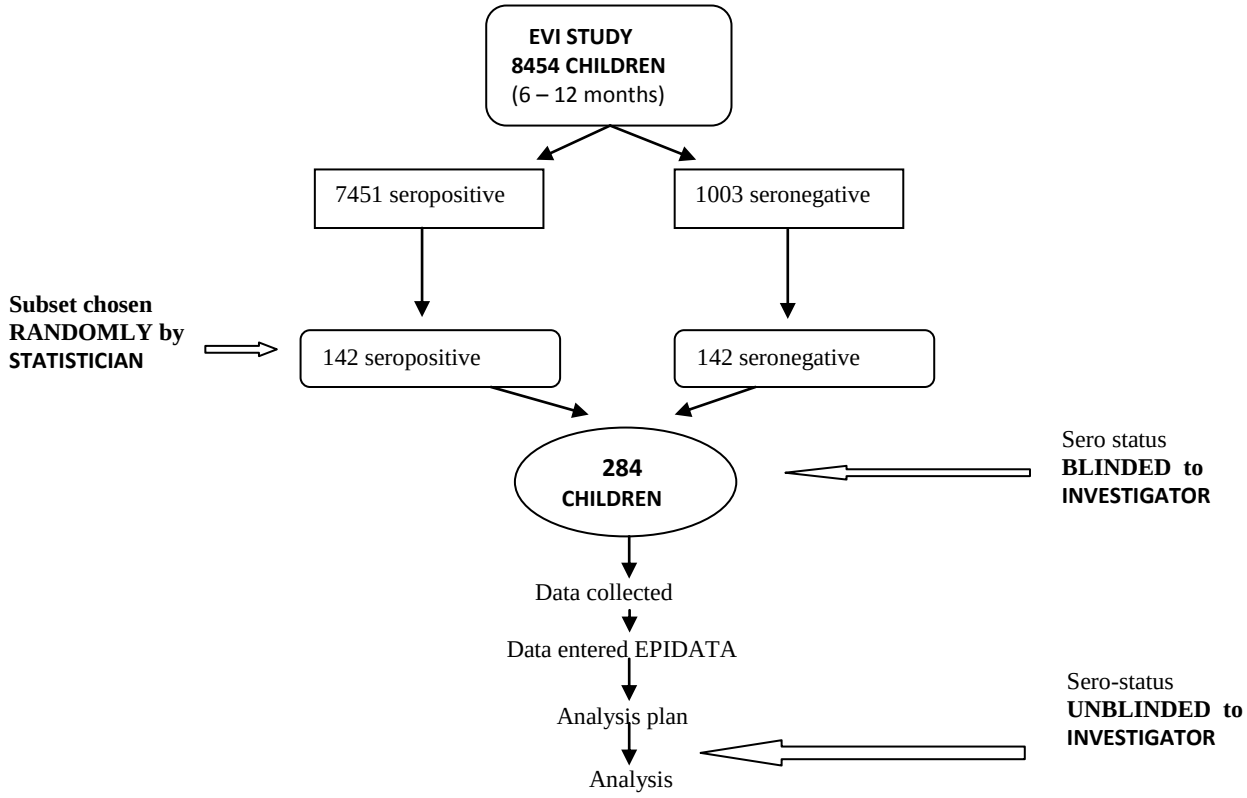
Power of the study is 80% i.e Zβ=0.842

Alpha error =5% i.e Zα=1.96

Data Collection

Study procedures were implemented as shown in the flow diagram below:

Figure 5.1 Study Procedure



The data collection tool had 3 components:

1. Structured questionnaire to identify risk factors applied to mothers/carers of children included in the study
2. Recording information on OPV detailed in the children's Immunization Cards
3. Anthropometric assessments (weight and height/recumbent length) of study children to check the nutritional status

Data Management

Data was entered in Epidata and analyzed using Statacorp, Texus version 12.0

Data Analysis

Descriptive statistics were done using bar charts and histograms. Socio-demographic characteristics of cases and controls were compared using t-test (continuous variables), wilcoxon test (ordered categorical variables) and the chi-square test (binary variables and categorical variables that were not ordered. To explore unadjusted and adjusted risk factors for being a case, univariable and multivariable analysis using binary logistic regression was performed; odds ratios and their confidence limits were estimated.

6. RESULTS

In the following section, a descriptive analysis is first presented under separate sections; demographic factors, parental related factors, birth related factors, breast feeding related factors, anthropometric measurements, water and sanitation factors, and operational factors.

This is followed by a risk factor analysis in which a univariable and then a multivariable analysis is presented in similar sections.

6.1 DESCRIPTIVE ANALYSIS

6.1.1 DEMOGRAPHIC CHARACTERISTICS:

A total of 284 children were recruited in the study. Among them 142 were cases and 142 were controls. The largest percentage of children were in the 14 month age group, with equally high percentages (15%) in the 13 and 15 months age group. The mean age in months was 15.

Mean age was 16 months in the control group and 15 months in the case group. (p=0.0009).

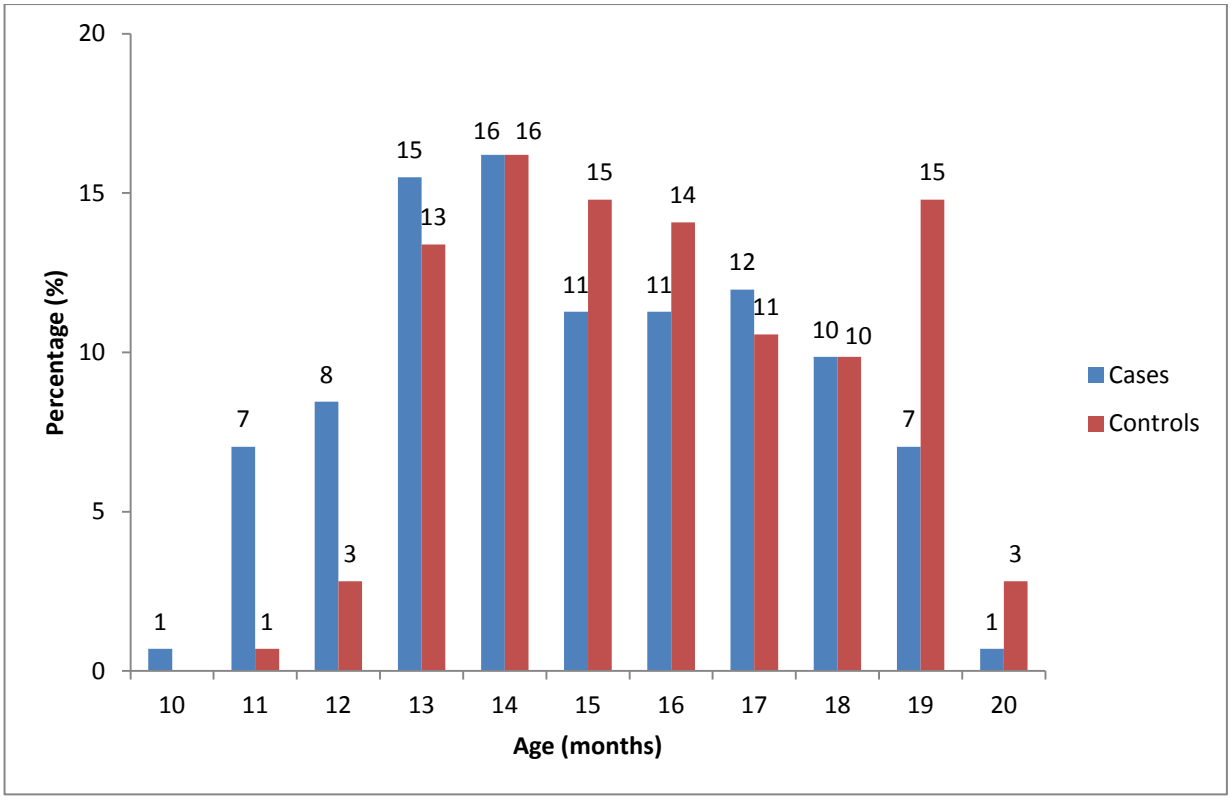


Figure 6.1 Age Distribution of the Study Population (cases n= 142, controls n=142)

Comparison of cases and controls for demographic factors are shown in Table 6.1

Amongst both the cases and the controls, about half were male children and most were from the rural area. Majority of the children from both the groups lived in pucca houses.

Majority of the children belonged to the most backward class, with 42% amongst the cases and 45% amongst the controls, followed by the scheduled class or tribe and other or backward class. Eighty one percent of the children belonged to the Hindu religion.

Table 6.1. Demographic Risk Factors by Seroprotection Status[*]

VARIABLE	CATEGORIES	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
Gender	Male	71(50)	79 (56)
	Female	71 (50)	63 (44)
Residence	Urban	62 (43.7)	57 (40)
	Rural	80 (56.3)	85 (60)
Type of House	Pucca	105 (73.9)	96 (67.6)
	Mixed	30 (21.1)	44 (31)
	Kutcha	7 (4.9)	2 (1.4)
Caste	OC/BC	34 (24)	30 (21.4)
	MBC	60 (42)	63 (45)
	SC	48 (34)	47 (33.6)
Religion	Hindu	113 (79.6)	116(81.7)
	Muslim	24(16.9)	23(16.2)
	Christian	5(3.5)	3(2.1)
SES	Upper Lower	44 (31.2)	44 (31)
	Lower Middle	55 (39)	63 (44.4)
	Upper Middle	38 (27)	33 (23.2)
	Upper	4 (2.8)	2 (1.4)

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

According to the Kuppuswamy scale, majority of the children belonged to lower middle socioeconomic background, with 39% in the cases and 44.4% in the controls. This is followed by the upper lower, upper middle and upper class. There were no children in the lower class.

There is no evidence to suggest a difference between the cases and controls with gender, residence, type of house, caste, religion or socio economic status (Kuppuswamy scale).

6.1.2 PARENTAL CHARACTERISTICS:

Comparison table of cases and controls with regard to parental factors are found in Tables 6.2-6.4

Mean age of the mothers is 25 years, as shown in Table 6.2, with the majority completing their high school, 38.7% amongst cases and 36% amongst the controls. Majority of the women were housewives, 81.7% amongst cases and 88% amongst the controls (Table 6.3).

Table 6.2 Mother's Age by Seroprotection Status[*]

VARIABLE	CASE/CONTROL	MEAN	STD. DEVIATION
Mother's Age	Case (N=142)	25.5	3.9
	Control (N=142)	24.9	3.9

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

The majority of the fathers completed their high school and are mainly unskilled workers as seen in Table 6.4

There is no evidence to suggest a difference between the cases and controls with regard to mother's age, mother's education, mother's occupation father's education or occupation.

Table 6.3 Mother's Education and Occupation by Seroprotection Status[*]

EDUCATION	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
Illiterate	6 (4.2)	6 (4.2)
Primary	9 (6.3)	6 (4.2)
Secondary	44 (31)	33 (23.2)
High School	55 (38.7)	51 (36)
Higher Secondary	19 (13.3)	29 (20.4)
Diploma/Degree/ Postgraduate	9 (6.3)	17 (12)
OCCUPATION		
Housewife	116 (81.7)	125 (88)
Skilled	3 (2.1)	3 (2.1)
Unskilled	19 (13.3)	11 (7.8)
Service related	1 (0.7)	0
Business	0	1 (0.7)
Professional	3 (2.1)	2 (1.4)

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.4 Father's Education and Occupation by Seroprotection Status[*]

EDUCATION	CASE (N=142) n (%)	CONTROL (N=142) n (%)
Illiterate	10 (7)	5 (3.5)
Primary	19 (13.5)	17 (12)
Secondary	35 (24.8)	31 (21.8)
High School	52 (36.9)	56 (39.4)
Higher Secondary	16 (11.4)	23 (16.2)
Diploma/Degree/ Postgraduate	9 (6.4)	10 (7)
OCCUPATION	**N=141**	**N=142**
Skilled	74 (52.5)	74 (52.1)
Unskilled	46 (32.4)	44 (31)
Service related	7 (5.0)	8 (5.6)
Business	7 (5.0)	14 (9.9)
Professional	6 (4.2)	2 (1.4)
Unemployed	1 (0.7)	0

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

6.1.3 SOCIOECONOMIC STATUS CHARACTERISTIC:

Comparison of the socioeconomic details is shown in table below. The average income per month was between Rs. 4770-7153. The majority of the cases and controls didn't have any land. Majority were in the upper middle group as seen in the figure below (Figure 6.2). SES did not appear to modify the risk of being a case.

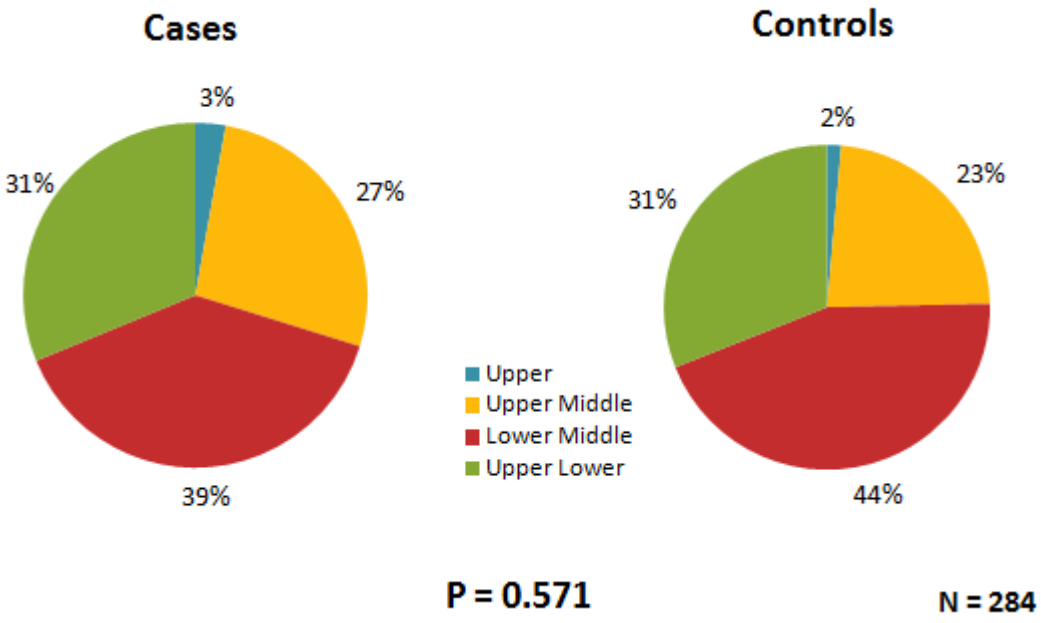


Figure 6.2 Kuppuswamy Scale for SES by Seroprotection Status[*]

6.1.4 IMMUNIZATION HISTORY:

The place of receiving their immunization is given in Figure 6.3. Majority of the children received their doses at a government hospital with the fourth dose given nearly equally at balwadi/school (42%) and at the government hospitals (47%).

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

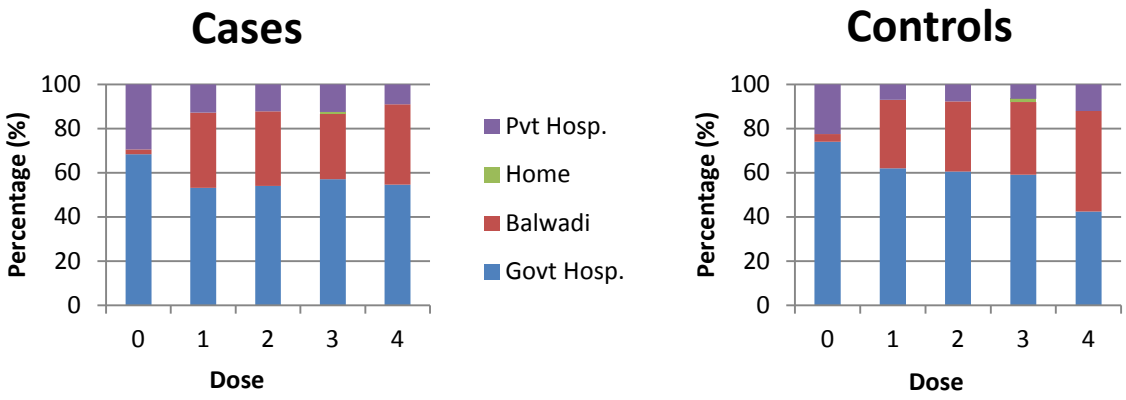


Figure 6.3 Place of Immunization by Seroprotection status[*]

Figure 6.4 and Table 6.5 show the number of doses for cases and controls. Majority of the children had 4 doses, 52.1% in the cases and 45% in the controls, with the difference being statistically significant with a p value of 0.017.

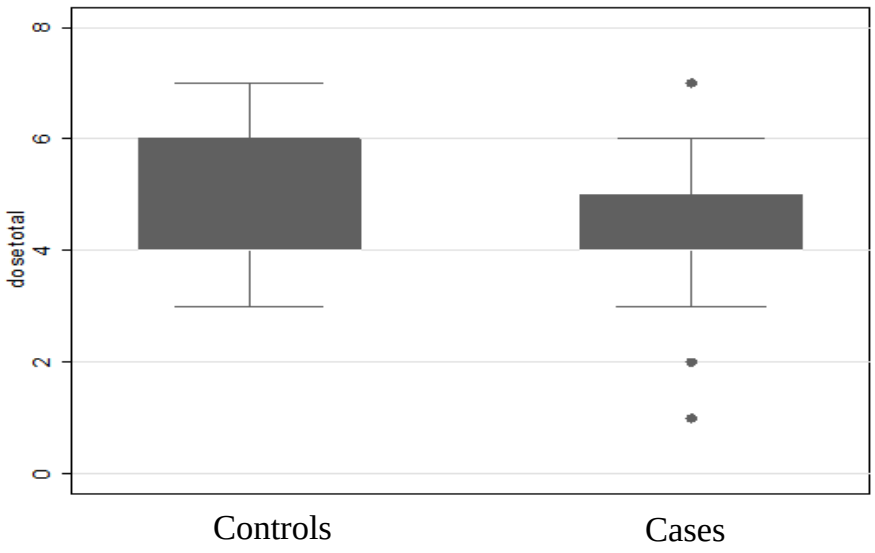


Figure 6.4 Total doses of OPV in cases and controls

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.5 Percentage of total doses by Seroprotection Status[*]

TOTAL NO. DOSES	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
1	1 (0.7)	0
2	3 (2.1)	0
3	11 (7.8)	8 (5.6)
4	74 (52.1)	64 (45)
5	22 (15.5)	25 (17.6)
6	30 (21.1)	42 (29.6)
7	1 (0.7)	3 (2.1)

6.1.5 BIRTH RELATED CHARACTERISTICS OF THE STUDY CHILDREN

Birth weights is shown in Table 6.6, Figure 6.5, place of birth in 6.8 and a comparison of low birthweight versus normal weight is seen in Table 6.7.

6.1.5. Birth weight of study children

The mean birth weight among cases and controls was 2.9 kg (±0.43 and ±0.44) respectively, shown in Figure 6.5 . There was no evidence to show a difference between the cases and controls (p=0.474).

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

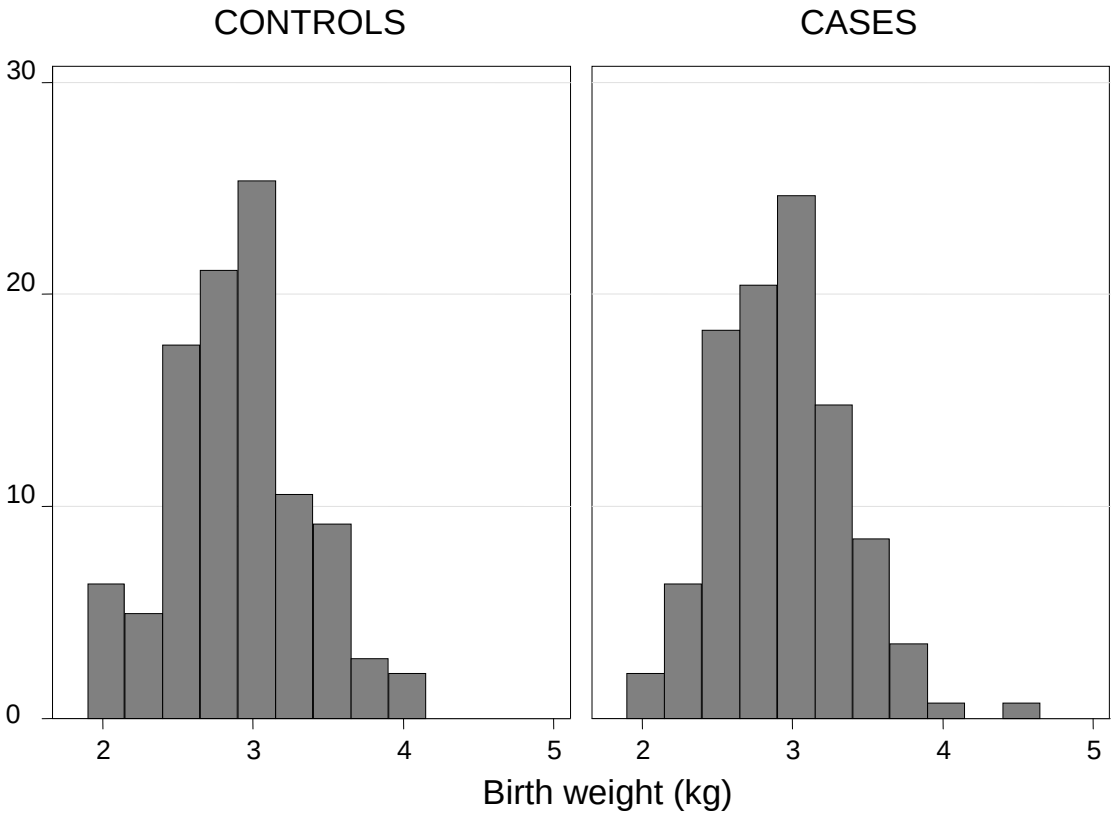


Figure 6.5 Birth Weight by Seroprotection Status[*]

Table 6.6 Birth Weight by Seroprotection Status[*]

	Mean Birthweight (kg)	**Standard Deviation**
Case (n= 142)	2.9	0.43
Control (n=142)	2.9	0.44

A total of 37 children were low birth weight, with 12% amongst the cases and 14% amongst the controls. There is no evidence to suggest any difference.

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

*Table 6.7 Low Birth Weight by Seroprotection Status**

	CASES (N= 142) n (%)	CONTROLS (N= 142) n (%)	P value
Low Birth Weight (<2.5kg)	17 (12)	20 (14)	0.597
Normal >/=2.5kg	125 (88)	122 (86)	

The majority of the cases and controls had a normal birth weight, 88% and 86% respectively. There was no evidence to suggest any difference.

Place of Birth (Govt/Private) of the study children:

The majority of the cases and controls were born in government hospitals, 68.3% and 67.6% respectively. There was no evidence to suggest any difference.

*Table 6.8 Place of Birth of Study Children by Seroprotection Status**

	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
Government Health Facility	97 (68.3)	96 (67.6)
Private Health Facility	45 (31.7)	46 (32.4)

The presence of other siblings showed no statistical difference between the cases and controls as seen in the Table 6.9. Majority had either one or no other siblings, with no evidence of association.

* *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.9 Presence of other siblings <5yrs age by Seroprotection Status[*]

OTHER SIBLINGS (<5yr olds)	CASES ((N=142) n (%)	CONTROLS (N=142) n (%)
0	68 (47.9)	75 (52.8)
1	68 (47.9)	62 (43.7)
2	6 (4.2)	4 (2.8)
3	0	1 (0.7)

6.1.5. Feeding practices of the study children:

Comparison of the feeding practices between the cases and controls are shown in table 6.10 and 6.11.

The mean number of months of exclusive breast feeding was 4 months (±2.13), with a min of 0 months to a maximum of 19 months. The mean number of months of exclusive breast feeding was 4 months (±2.13), with a min of 0 months to a maximum of 19 months. The majority of the cases (99.3%) and controls (96.5%) were given colostrum. There is no statistical evidence of any difference between the cases and controls with regard to feeding practices.

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.10 Feeding Practices by Seroprotection Status[*]

FEEDING PRACTICES	DURATION (months)	CASES (N = 142) n (%)	CONTROLS (N = 142) n (%)	Mean – months (SD)
Exclusive Breast feeding	**0-3**	62 (43.7)	57 (40.1)	4.0 (±2.1)
	4-6	69 (48.6)	76 (53.5)	
	7-12	10 (7)	9 (6.3)	
	≥13	1 (0.7)	0	
Initiation of of Complementary Feeds	**0-3**	20 (14.1)	10 (7)	5.9 (±2.2)
	4-6	81 (57)	87 (61.3)	
	7-12	40 (28.2)	45 (31.7)	
	≥13	1 (0.7)	0	
Initiation of Water	**0-3**	25 (17.6)	24 (16.9)	5.6 (± 2.2)
	4-6	72 (50.7)	83 (58.5)	
	7-12	44 (31)	33 (23.2)	
	≥13	1 (0.7)	2 (1.4)	

Table 6.11 Feeding Colostrum by Seroprotection Status[*]

	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
Given	141 (99.3)	137 (96.5)
Not given	1 (0.7)	5 (3.5)

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

6.1.6. MEDICAL HISTORY OF THE STUDY CHILDREN

Comparison of the medical history with regard to the variables admission, reason for admission and presence of diarrhoea at the time of receiving OPV is shown in Tables 6.12 - 6.14. Being admitted did not increase the chance of being a case.

Table 6.12 Admission to a Hospital by Seroprotection Status[*]

	CASES (N=142) n (%)	**CONTROLS (N=142) n (%)**
Yes	25 (17.6)	24 (16.9)
No	117 (82.4)	118 (83.1)

Majority of cases and controls did not have diarrhoea at the time of receiving adose of OPV (Table 6.14). There was no evidence to show any difference.

Table 6.13 Reasons for Admission to the Hospital by Seroprotection Status[*]

	CASES (N=25) n (%)	**CONTROLS (N=24) n (%)**
Pneumonia	7 (28)	13 (54.17)
Diarrhoea	4 (16)	0
Febrile Seizures	2 (8)	3 (12.5)
Others	12 (48)	8 (33.33)

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.14 Presence of Diarrhoea at the time of receiving an OPV Dose by Seroprotection Status[*]

	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
Yes	2 (1.4)	1 (0.7)
No	140 (98.6)	141 (99.3)

6.1.7. ANTHROPOMETRIC MEASUREMENTS OF THE STUDY CHILDREN

Tables 6.15 – 6.16 show the anthropometric measurements. The z scores between cases and controls were found to show some evidence for a difference with regard to height for age score, with a difference of 0.2 and a P value of 0.097 as seen in Figure 6.6 and Table 6.15.

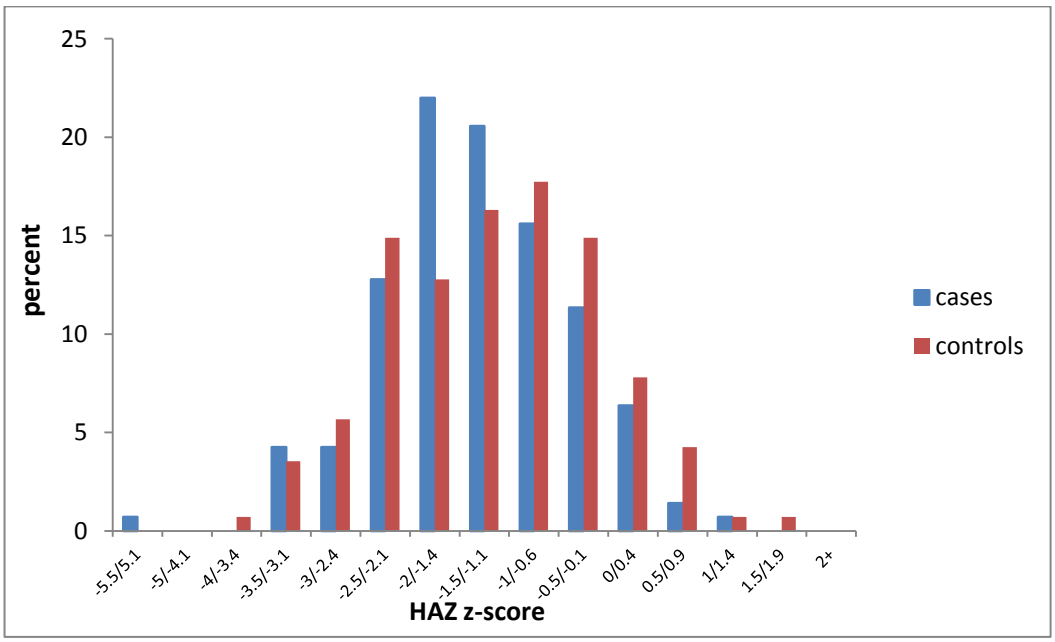


Figure 6.6 Height for age z scores by Seroprotection Status[*]

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.15 Mean Z scores by Seroprotection Status[*]

Z-SCORE SYSTEM	CASES (mean)	CONTROLS (mean)	DIFFERENCE	P VALUE
WHZ	-0.83	-0.85	-0.01794	0.875
WAZ	-1.26	-1.16	0.094	0.371
HAZ	-1.35	-1.15	0.2	0.097

Comparison of underweight, stunting and wasting (Table 6,16) by seroprotection status showed no evidence of any difference.

Table 6.16 Underweight, Stunting and Wasting by Seroprotection Status[*]

	CASES n (%)	CONTROLS n (%)
Underweight (WHZ<-2)	18 (12.8)	13 (9.2)
Stunting (HAZ<-2)	31 (22)	35 (24.8)
Wasting (WAZ<-2)	26 (18.3)	29 (20.4)

6.1.8. WATER & SANITATION CHARACTERISTICS :

Factors related to water and sanitation, such as sanitary practices, source of drinking water, treatment of drinking water, time taken to reach the water source, and treatment of water given to the child at the time of initiating water into the diet were looked into.

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Open defecation was practiced by 50% amongst cases and 47.2% in the control as seen in Table 6.17 , followed by private toilets (cases: 42.3% and controls 46.5%), and shared toilets being the least common.

Table 6.17 Sanitary Practices by Seroprotection Status[*]

	CASES (N=142) n (%)	**CONTROLS (N=142) n (%)**
TOILET	60 (42.3)	66 (46.5)
SHARED LATRINE	11 (7.8)	9 (6.3)
OPEN DEFECATION	71 (50)	67 (47.2)

As shown in Table 6.18, open defecation was more common in the rural area with 70% as opposed to 18% in the urban area.

Table 6.18 Comparison of the practice of Open Defecation between Rural and Urban areas.

OPEN DEFECATION	**RURAL (N=165) n (%)**	**URBAN (N=119) n (%)**
Yes	116 (70.3)	22 (18.49)
No	49 (29.7)	97 (81.51)

Initiation of water to the child was mainly between 4-6 months, cases with 50.7% and controls with 58.5%. The majority did not treat the water given to the child at

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CONTROL- Children who are seroprotected against type 3 poliovirus

the time of initiating water in the feeds, cases with 73.8% and controls with 64.8%.

There was some evidence of the treatment of water with being a case (p=0.102).

Table 6.19 Treatment of Drinking Water given to the child by Seroprotection Status[*]

	CASES (N=141) n (%)	**CONTROLS (N=142) n (%)**
Treated	37 (26.2)	50 (35.2)
Not treated	104 (73.8)	92 (64.8)

The source of water was mainly a government supply amongst cases and controls, 80.3% and 81% respectively, with the majority of them not treating this water prior to drinking . The source of water was in the majority of the cases and controls outside their houses, with access to water less than 5 minutes away in the majority of the households, as seen in Table 6.20. There is no evidence to show any difference between the above variables between the cases and controls.

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.20 Source of Household Drinking Water by Seroprotection Status[*]

	CASES (N=142) n (%)	**CONTROLS (N=142) n (%)**
Piped(govt)	114 (80.3)	115 (81)
Borewell	8 (5.6)	6 (4.2)
Dug well/ Spring water	1 (0.7)	1 (0.7)
Water tanker	7 (4.9)	7 (4.9)
Bottled	12 (8.5)	13 (9.2)

Table 6.21 Treatment of Household Drinking Water by Seroprotection status[*]

	CASES (N=142) n (%)	**CONTROLS (N=142) n (%)**
No treatment	122 (85.9)	116 (81.7)
Boiling	17 (12)	21 (14.8)
Household water Treatment	3 (2.1)	5 (3.5)

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CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.22 Time taken to the Water Source by Seroprotection status[*]

TIME (mins)	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
0	50 (35)	51 (36)
2	42 (30)	54 (38)
5	32 (23)	21 (15)
10-15	13 (9)	13 (9)
>15	5 (4)	3 (2)

6.1.9. OPERATIONAL FACTORS OF THE STUDY POPULATION

Two questions were asked about the village health nurse, firstly if they knew her and secondly if they were able to name her. This was seen as a proxy for access to the health system and / or social inclusion. Majority of the cases (77.5%) and controls (83.8%) knew the VHN and 55.6% of the cases and 65.5% of the controls were able to name the VHN as seen in Table 6.23. There was some evidence to show an association with being a case and familiarity with naming the village health nurse (p= 0.089).

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.23 Familiarity with the Village Health Nurse by Seroprotection Status[*]

	YES/NO	CASES (N=142) n (%)	CONTROLS (N=142) n (%)
Know VHN	**YES**	110 (77.5)	119 (83.8)
	NO	32 (22.5)	23 (16.2)
Named VHN	**YES**	79 (55.6)	93 (65.5)
	NO	63 (44.4)	49 (34.5)

6.2. RISK FACTOR ANALYSIS

Various risk factors were analyzed to assess the association with being a case. Results are presented under separate sections as demographic factors, parental related factors, birth related factors, breast feeding related factors, anthropometric factors, water and sanitation factors, and operational factors.

6.2.1. UNIVARIABLE ANALYSIS:

PER DOSE PROTECTION- The odds ratio of being a case with every increase in a dose was calculated to be 0.74 (95% C.I.: 0.59 – 0.93), suggesting a decrease in the odds of being a case with every additional dose. Assuming that the odds

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CONTROL- Children who are seroprotected against type 3 poliovirus

ratio will be close to the risk ratio, the per dose protection was calculated as 1-OR= 26% (95% C.I.:7% - 41%). Figure 6.5 depicts the possible vaccine efficacies with every additional dose. This is calculated based on the formula VE2= VE1 + (VE1 (100-VE1), VE3= VE2 + (VE1 (100-VE2))(89), where VE1,2,n denotes vaccine efficacy after dose 1, 2,n.

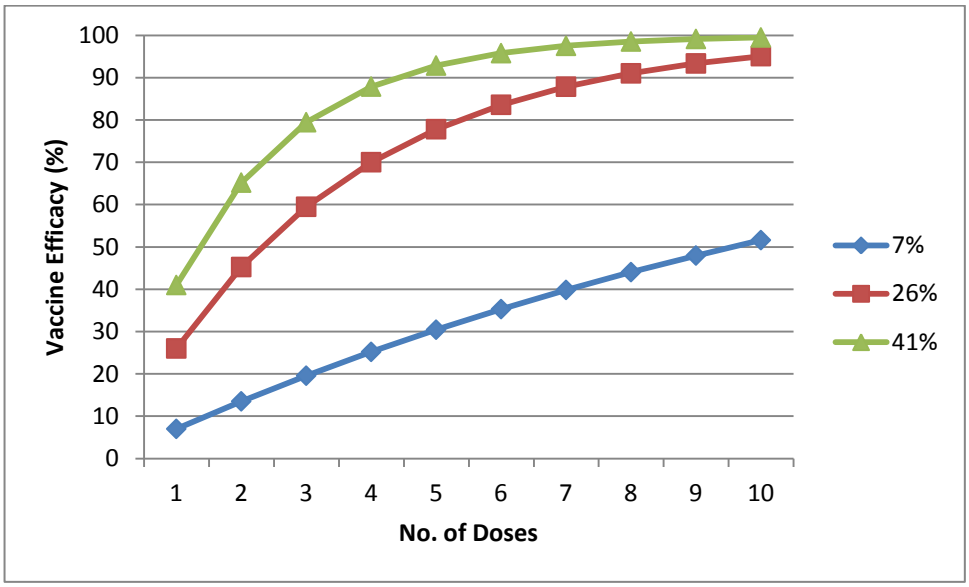

Figure 6.7 Vaccine Efficacy versus No. of Doses

DEMOGRAPHIC RISK FACTORS

Gender, area of residence, type of house, religion, caste and SES were categorized and analysed for associations with lack of seroprotection. None of the variables amongst demographic related risk factors showed any consistent association with being a case

Table 6.24 The effect of demographic factors on the Lack of Seroprotection[*]

VARIABLE	CASES N=142 n (%)	CONTROLS N = 142 n (%)	OR (95% C.I.)	P – values
Gender				
Male	71 (50)	79 (56)	(Ref)	
Female	71 (50)	63 (44)	1.25 (0.79 - 2.00)	0.342
Area of Residence				
Rural	62 (43.7)	57 (40)	(Ref)	
Urban	80 (56.3)	85 (60)	1.16 (0.72 - 1.85)	0.548
Type of House				
Pucca	105 (73.9)	96 (67.6)	(Ref)	
Kutcha/Mixed	37 (26.1)	46 (32.4)	0.74 (0.44 – 1.23)	0.24
Religion				
Others	118 (83.1)	119 (83.8)	(Ref.)	
Muslim	24 (16.9)	23 (16.2)	1.05 (0.56 - 1.97)	0.873
SES (Kuppuswamy Scale)	**N=141**	**N=142**		
Middle/Upper	97 (68.8)	98 (69)	(Ref.)	
Lower upper	44 (31.2)	44 (31)	1.01 (0.61 – 1.67)	0.968
Caste	**N = 142**	**N =140**		
OC/BC/MBC	94 (66.2)	93 (66.4)	(Ref.)	
SC	48 (33.8)	47 (33.6)	1.01 (0.62 -1.66)	0.967

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

The odds ratios were for female 1.25 (95% C.I.:0.79 - 2.00), urban 1.16 (95% C.I.:0.72 - 1.85), Kutcha/mixed 0.74 (95% C.I.:0.44 – 1.23), Muslim 1.05 (95% C.I.: 0.56 - 1.97), lower upper SES (Kuppuswamy group) 1.05 (95% C.I.:0.56 - 1.97) and being in the Schedule caste 1.01 (95% C.I.: 0.62 -1.66).

PARENTAL RELATED RISK FACTORS

Amongst the parental related risk factors, the decrease in the odds of being a case per additional of year of mother's education was 0.92 with a 95% confidence interval of 0.86-0.99 as seen in Table 6.26. For all other factors, there was little statistical evidence for an association.

Table 6.25 The effect of parental factors on Lack of Seroprotection[*]

VARIABLE	CASES (N=142) n (%)	CONTROLS (N=142) n (%)	OR (95%C.I.)	P – value
Mother's Education				
9th & above	83 (58.4)	97 (68.3)	(Ref)	
None – 8th std	59 (41.6)	45 (31.7)	1.53 (0.94 - 2.49)	0.085
Mother's Occupation				
Housewife	116 (81.7)	125 (88)	(Ref.)	
Working	26 (18.3)	17 (12)	1.65 (0.85 – 3.19)	0.139
Father's Occupation	**N=141**	**N=142**		
Others	95 (67.4)	98 (69)	(Ref.)	
Unskilled	46 (32.6)	44 (31)	1.08 (0.65 – 1.78)	0.767

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

*Table 6.26 The effect of Parental Education (in years) on Lack of Seroprotection**

	Coefficient	OR (95% C.I.)	P value
Mother's Education (total yrs)	-.0791721	0.92 (0.86- 0.99)	0.034
Father's Education (total years)	-.0008674	1 (0.96 - 1.04)	0.963

BIRTH RELATED RISK FACTORS

In the birth related risk factors, all variables including place of birth and birth weight and the presence of other siblings showed no association as seen in table 6.33 and 6.34. The odds of a private health facilty birth as compared to government health facility on lack of seroprotection was 0.97 with the confidence interval crossing 1. Similarly with low birth weight and having more than one sibling as a risk factor for having lack of seroprotection was 0.83 and 1.2, with a 95% C.I. crossing 1.

*Table 6.27 The effect of Birth related factors on Lack of Seroprotection**

VARIABLE	CASES N=142 n (%)	CONTROLS N=142 n (%)	OR (95% C.I.)	P - values
Birth – at Private Health Facility	45 (31.7)	46 (32.4)	0.97(0.59 – 1.59)	0.899
Low Birth weight	17 (12)	20 (14)	0.83 (0.41 – 1.66)	0.597
Having ≥1 Sibling	74 (52.1)	67 (47.2)	1.2 (0.76 – 1.94)	0.406

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BREAST FEEDING RELATED RISK FACTORS

In the breast feeding related risk factors, few of the variables showed any consistent association with being a case, including duration of exclusively breast feeding and initiation of water. There was however a trend towards introduction of complementary food after 4 months. The odds of being a case increased by a factor of 2 with a 95% C.I.: 0.97 -1.67, when complementary feeds were given before 4 months.

Table 6.28 The effect of Feeding practices on Lack of Seroprotection[*]

VARIABLE	CASES (N=142) n (%)	CONTROLS (N=142) n (%)	OR (95% C.I.)	P - value
Breast Feeding				
≥ 6 months	26 (18.3)	24 (16.9)	(Ref.)	0.755
0 - 6 months	116 (81.7)	118 (83.1)	0.91 (0.49 – 1.67)	
Complementary Feeds				
≥4 months	122 (85.9)	132 (93)	(Ref.)	0.058
0-4 months	20 (14.0)	10 (7)	2.16 (0.97 - 4.81)	
Initiation of Water in Diet				
≥4 months	117 (82.4)	118 (83.1)	(Ref.)	0.875
0-4 months	25 (17.6)	24 (16.9)	1.05 (0.57 – 1.94)	
Colostrum given	141 (99.3)	137 (96.5)	5.15 (0.59 - 44.62)	0.137

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CONTROL- Children who are seroprotected against type 3 poliovirus

ANTHROPOMETRIC MEASUREMENT RELATED RISK FACTORS:

Amongst the anthropometric variables, there was some trend that each additional z-score of height-for-age decreased the odds of being a case (by about 18%), but the confidence interval just crossed the point of equivalence. To a lesser extend this trend was also observed for weight-for-age z scores. However, using established cut off points of these anthropometric measures (stunting, underweight, wasting) did not result in clinically relevant associations.

Table 6.29 The effect of Anthropometric related factors on Lack of Seroprotection[*]

VARIABLE	ODDS RATIO	95% CONFIDENCE INTERVAL	
WHZ	1.02	0.80	1.30
HAZ	0.82	0.65	1.04
WAZ	0.89	0.68	1.15

Similarly, there was no effect of stunting, wasting or being underweight on lack of seroprotection as seen in Table 6.30. The O.R. were 0.85 (95% C.I.:0.49 – 1.48) for stunting, 0.87 (95% C.I.: 0.48 – 1.57) for wasting and 1.44 (95% C.I.:0.68 – 3.07) for being underweight.

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.30 The effect of Stunting,Underweight and Wasting on Lack of Seroprotection[*]

VARIABLE	CASES n (%)	CONTROLS n (%)	OR (95% C.I.)	P – value
Stunting	**N =141**	**N = 141**		
No	110 (78)	106 (75.2)	(Ref.)	
Yes	31 (22)	35 (24.8)	0.85 (0.49 – 1.48)	0.574
Underweight	**N=141**	**N= 141**		
No	123 (87.2)	128 (90.8)	(Ref.)	
Yes	18 (12.8)	13 (9.2)	1.44 (0.68 – 3.07)	0.343
Wasting	**N=142**	**N=142**		
No	116 (81.7)	113 (79.6)	(Ref.)	
Yes	26 (18.3)	29 (20.4)	0.87 (0.48 – 1.57)	0.652

WATER & SANITATION RELATED RISK FACTORS:

In the water and sanitation related factors, none of the variables including sanitary practices, water source and treatment of water showed a clear association. There was however, some evidence that feeding treated water to the child at the time of initiating water feeding decreases the odds of lack of seroprotection.

The odd ratio was 1.53, with the 95% confidence interval 0.92 – 2.54.

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

Table 6.31 The effect of Water and Sanitation related factors on Lack of Seroprotection[*]

VARIABLE	CASES (N=142) n (%)	CONTROLS (N=142) n (%)	OR (95% C.I.)	P value
Sanitary Practices				
Toilet	71 (50)	75 (53.8)	(Ref.)	
Open Defecation	71 (50)	67 (47.2)	1.12 (0.70 – 1.78)	0.635
Household Drinking Water Source				
Piped/Tap	114 (80.3)	115 (81.0)	(Ref.)	
Others	28 (19.7)	27 (19.0)	1.05 (0.58 – 1.88)	0.881
Household Drinking Water Treatment				
Yes	20 (14.1)	26 (18.3)	(Ref.)	
No	122 (85.9)	116 (81.7)	1.37 (0.72 – 2.58)	0.335
Feeding treated water to child – (at time of initiating water)				
Yes	37 (30.7)	50 (35.2)	(Ref)	
No	104 (73.8)	92 (64.8)	1.53 (0.92 – 2.54)	0.103

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

OPERATIONAL RELATED RISK FACTORS

Operational factors were studied, looking particularly at the distance to the health centre in terms of time taken to reach the centre, adjusting for the number of doses. In linear regression it was found that there was no relation with time taken to the vaccination centre and number of doses. Coefficient was -0.0036 (95% C.I.:-0.0083 – 0.0011), with a p value of 0.13 and R squared = 0.008, suggesting a lack of an association.

Knowing the village health nurse (VHN) and being able to name the VHN was also looked at as a proxy marker of the link to the health system. Not able to name the VHN was found to increase the odds of being a case by 1.51 with the confidence interval just crossing 1 (0.94 – 2.44).

Table 6.32 The effect of not being able to name the VHN on Lack of Seroprotection[*]

VARIABLE	CASES N=142 n (%)	CONTROLS N=142 n (%)	OR (95% C.I.)	P value
Not able to name VHN	63 (44.4)	49 (34.5)	1.51 (0.94 – 2.44)	0.090

[*] *CASE - Children who are not seroprotected against type 3 poliovirus*
CONTROL- Children who are seroprotected against type 3 poliovirus

6.2.2. MULTIVARIABLE ANALYSIS:

A multivariable analysis was done building a complete model including all variables with $p \leq 0.1$ in univariable analysis (gender and SES were included for completeness despite $p > 0.1$), as shown in Table 6.33. The following variables were included: mother's occupation, mother's education, giving colostrum, treatment of water at time of initiating drinking water for the child, height for age z score, not naming the village health nurse, age in months and total number of doses. Here again age and total number of doses were chosen as potential confounder to be adjusted for as these showed strong associations with vaccine failure (= being a case). Age of weaning was dichotomized into 0-4 months and 4 as added into the model.

Giving colostrum became a significant variable after adjusting for all the other variables, with an odds ratio of 10.35 (95% C.I.: (1.03 – 104.40). Further, there was evidence that a working mother, inability to name the village health nurse increased the odds of lack of seroprotection. There was also some evidence that early weaning roughly doubled the odds of lack of seroprotection.

Table 6.33 Joint effects of risk factors on lack of seroprotection adjusted in a multivariable logistic model

	Unadjusted OR (95% C.I.)	**Adjusted OR (95% C.I.)**	**P value**
Female	1.25 (0.79 - 2.00)	1.31 (0.78 – 2.18)	0.293
Mother's Education: (in yrs)	0.92 (0.86- 0.99)	0.91 (0.84 – 0.99)	**0.034***
Working mother	1.65 (0.85 – 3.19)	2.11 (1.01- 4.4)	**0.047***
SES (Lower – upper)	1.01 (0.61 – 1.67)	0.78 (0.44 – 1.38)	0.402
Colostrum given	5.15 (0.59 – 44.62)	11.77 (1.21 – 114.89)	**0.034***
Weaning (<4months)	2.16 (0.97 - 4.81)	2.2 (0. 94 – 5.15)	0.068
Not feeding treated water to child	1.53 (0.92 – 2.54)	1.39 (0.80 – 2.44)	0.244
Height for Age Z scores (HAZ)	0.82 (0.65 – 1.04)	0.85 (0.66 – 1.11)	0.234
Not Naming VHN	1.51 (0.94 – 2.44)	1.70 (1.00 – 2.88)	**0.048***
Total Doses	0.74 (0.59 – 0.93)	0.81 (0.61 – 1.07)	0.134
Age (in months)	0.84 (0.76 – 0.93)	0.83 (0.73 – 0.95)	**0.005***

***statistically significant**

7. DISCUSSION

This thesis explored risk factors of poor immune response to OPV in a part-urban part rural low income population in a southern Indian state. The risk factors studied can be broadly classified as biological (e.g. nutritional status, age of weaning, feeding of colostrums), socio-economic (e.g. mothers education and occupation) and operational (e.g. time to reach institution in which OPV was given and familiarity with the VHN). The results of this thesis suggest that some of the explored biological (and therefore fairly proximal) potential risk factors, such as feeding colostrum, possibly low height-for-age z-score and early weaning were associated with vaccine failure. Further, there were trends towards several socio-economic factors such as maternal education, occupation and being able to name the village health nurse (possibly a proxy for access to the health system and / or social inclusion) being associated with vaccine failure. No evidence was found that other operational factors influenced vaccine efficacy.

Biological factors such as breastfeeding have shown to affect immune response (49), with a marked reduction to type 3 (54). However, other studies have shown an increase in OPV titres with additional months of exclusive breastfeeding (46). It has also been suggested that maternal antibodies reduce the efficacy of the first dose of OPV (72), which is later on mitigated by additional doses of OPV (72). Evidence suggests that exclusively breastfed children have higher anti polio IgA responses (46, 51). This thesis supports this idea, as those given colostrum were

found to have an increased odds of vaccine failure and those with an early period of weaning were found to also have an increased odds of vaccine failure. Introduction of complementary food before 4 months increased the odds of being a case by 2.2 times with 95% CI just crossing 1 (0.94—5.15). This result makes the case for breastfed children to be more protected after OPV.

Being female increased the odds of vaccine failure by 25% however the confidence interval was wide and crossed 1 (95% C.I.: 0.79 – 2.00). The literature with respect to gender as a biological factor for vaccine failure is equivocal. The evidence with respect to possible associations between gender and vaccine failure continues to be unresolved (50, 52).

The height of a child is an indirect indicator of the past nutritional status (54). Studies done in north India found malnutrition to be associated with a lower seroprevalence of antibodies to type 3 (59). Although a trend can be found in our study with height for age z scores, as it just crosses the point of equivalence, it makes nutrition an unresolved factor associated to vaccine failure. With every increase in height z-score the odds of vaccine failure decreased by 8%. The association found in this study was not strong, in line with the conflicting evidence from previous studies (54, 58-60). Therefore, poor nutritional status can explain only a small proportion of the frequent vaccine failure in poor settings.

Diarrhea has been shown in literature to be associated with reduced immunogenicity to type 3 poliovirus by 15% (48) and other studies showing 18% (53). A study done at Dhaka found diarrhoea to be a significant risk factor in

children in the first months after birth(65), however this effect was not clear in the third or fourth dose of OPV to type 3 in a study done at Brazil (59). The difference in the immunogenicity at different ages suggests a link to maternal antibodies which may add to the decreased immunogenicity at an early age and ware of with time. It also suggests that the child's immune system's capacity to mount a response improves with age.

Diarrhoea during OPV dose was a rare event in our study. As this question requires the mother to remember an event that might have occurred more than 6 months ago, it could be that this information is not clear enough to find an association that is seen in many previous studies (40, 65).

Some socioeconomic factors such as education and factors related to water and sanitation may affect immunogenicity (67, 68), and this was confirmed in this study especially with respect to mothers' education level. The causal pathway from maternal education to vaccine failure is likely to be highly complex, possibly involving issues of hygiene, nutrition, wealth and water/sanitation.

Our study found with every increase in the mother's education (in years), the odds of being a case decreased by 8%. When education was dichotomized into no education to secondary and high school and above education, the odds of being seronegative increased by 53% in those with a lower education with a 95% C.I. crossing 1, however suggesting a possible association with vaccine failure. However, one can say maternal education continues to rightly be a driving force in the prevention of many public health issues related to the child.

In the water and sanitation related factors, none of the variables including sanitary practices, water source and treatment of water didn't show any association. There appeared to be a trend with not treating water given to children at the time of initiation of water, with the odds of vaccine failure increases by 53% and a confidence interval just crossing 1 (0.92 – 2.54). However, this may be partially due to confounding by socio-economic factors and mothers education.

Naming the VHN can be seen as a proxy marker of accessibility to the delivery system and possibly social inclusion, indicating operational factors might be associated with vaccine failure. This study found some evidence to show an association with unfamiliarity with the village health nurse and being a case. Similar to maternal education the causal link between able to name the village health nurse and seroconversion is likely to be complex, and possibly subject to confounding.

8. LIMITATIONS

As evidenced by the fact that even some of the large effect sizes had confidence intervals crossing 1, the power to detect associations was still limited. A larger sample size would have been desirable.

The calculation of the per dose vaccine efficacy is limited by the underlying assumptions: first the calculation assumes a linear association between number of doses and seroconversion. Very few children in this study had fewer than 3 doses. A linear trend at these doses can therefore not be readily assumed. Above 2 doses, the effect however appeared linear. Second, the calculations assume that the odds ratio approximates the risk ratio which requires the rare disease assumption where odds ratio and risk ratio can be assumed to be similar.

Further limitations relate to the data quality. The vaccination history was recorded by the mothers' report and confirmed by vaccination card where available. The mothers' reporting was often unreliable as some of the mothers did not recall what vaccine had been given when. The vaccination cards were at times incomplete, and there were uncertainties whether vaccines were given or not (17%). However, combining data from verbal reports and vaccination cards should in the vast majority of cases provide us with reasonably accurate data on the number and approximate timing of OPV doses given. This is all the more the case as OPV as the only oral vaccine in the schedule and in contrast to other vaccines therefore had a good chance of being uniquely recognizable by mothers.

A further limitation relates to the observational nature of the study. Confounding is a common issue in these studies. Factors non-causally associated with being a case and with being exposed may exaggerate or dilute odds ratios especially in univariable analysis. For example, the association between not treating water given to children (OR 1,53) may be partially be due to confounding by socio-economic factors and mothers education. Accordingly, the association was weaker in the adjusted analysis (OR 1,39). Residual confounding may explain some of the remaining association.

The study was conducted in largely poor neighborhoods in Vellore town and villages throughout the district. Wealthier areas within Vellore were not included in the cohort from which children for this case control study were recruited. Therefore the results of this analysis are not necessarily representative for Vellore district as a whole, let alone for the state of Tamil Nadu or India. Nevertheless it is likely that similar associations may be found in other poor settings in India and elsewhere in South Asia or Africa, especially with respect to the biological factors studied.

Case-control studies are at risk of selection bias, as it can be difficult to sample controls that come from the same source population as the cases. However, in this study selection bias is unlikely to have occurred as the study was nested in a larger cohort of children. The case/control status was determined based on serological data, after the children had already been recruited into the cohort. The source population of cases and control can therefore, for most practical considerations, be assumed to be identical.

9. SUMMARY AND CONCLUSIONS

The study showed associations between several biological factors and failure to mount an adequate immune response following OPV. Some of these risk factors are modifiable. In line with current public health policy, early weaning should be discouraged. The association between colostrum and vaccine failure appears to be high. However, giving colostrum is generally recommended to protect the child against common neonatal and infant infections such as pneumonia and diarrhea that carry a far higher risk of death than Polio. The finding from this and other studies of an increased risk of vaccine failure due to colostrums should therefore not change breastfeeding public health policy. Further public health measures to combat diarrhoeal diseases and malnutrition could contribute to improved immune response to OPV. In this context the socio-economic risk factors explored in this thesis are of interest as these can be regarded as upstream factors that modify the risk of ill health via many different pathways.

Maternal education appears to contribute at least to some extent to the poor response to OPV in poor settings in India. These factors are also strongly associated with environmental enteropathy, a condition that recently has gained renewed interest in the research community because of its strong link with malnutrition and failure to thrive (67). Environmental enteropathy may impair mucosal response to gastrointestinal infection including infection with OPV. It may partially explain the association between various socio-economic factors and lack of seroprotection following OPV.

Inequalities in wealth distribution, social inclusion, education and health care access continue to be the main factors for ill health in India even as the country on average becomes richer (90, 91). This thesis suggests that these mechanisms may extend to the immune response to oral polio vaccination.

10. RECOMMENDATIONS

This study shows some evidence of early weaning as a risk factor for vaccine failure. Efforts to promote exclusive breastfeeding should therefore be supported also from the perspective of OPV efficacy. Other risk factors identified in this study especially those related to socio-economic and educational factors are complex and unlikely to be easy targets for public health policy interventions. Until the question of social inequality is sustainably addressed, the policy of giving many repeat doses of OPV will continue to be required in low income settings across India in order to maintain sufficient levels of immunity to prevent re-emergency of polio.

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12. ANNEXURES

Annexure 1 - STUDY PROFORMA

NO	QUESTION	RESPONSE
1	Rural/Urban	Rural……..1 Urban……..2
2	Village Name/ Ward Name	Village (specify)_____ Ward (specify)_____
3	Interview Date	I___.___I___.___I___.___I DD MM YY
4	Who is the primary Caregiver	Mother……..1 Grandmother……..2 Others (specify)_____..3
5	Agree to participate:	Yes……1 No……0
	MATERNAL HISTORY	
6	Age	(yrs)
7	Education of Mother	
8	Occupation of Mother	
9	Number of children below 5 yrs of age (excluding study child)	

		(no.)
	BIRTH HISTORY	
10	Date of birth	I___.___I___.___I___.___I DD MM YY
11	Place of Birth	
12	Gender	Male……1 Female……..2
13	Birthweight	I_____._____I kg
14	Source Document (Birthweight)	ANC Card ……..1 Immunization Card…2 ANC Notebook……..3 Others……..4

IMMUNIZATION HISTORY OF CHILD:

15.CardAvailable:Y/N

Q.No.	OPV	DATE GIVEN (from CARD)	AGE ADMINISTERED (MONTHS) (by history, when card absent)	PLACE ADMINISTERED (write in words) Specify		LENGTH TIME TO REACH (mins)	MODE
16.	0						
17.	1						
18.	2						
19.	3						
	4						
	ADDITIONAL DOSES	DATE GIVEN	NID/ Non NID	PLACE ADMINISTERED		Documented(Y/N)	If yes, Image no.
20.	1						
21.	2						
22.	3						

23. Immunization (UIP) appropriate for age – other vaccines timely given

Yes……..1
No……..0

24 .IMMUNIZATION HISTORY OF OTHER LIVING CHILDREN: (Routine Immunizations – 4 doses OPV)

CHILD	Complete : Y/ N	Card present :Y/N
1		
2		
3		
4		

	BREASTFEEDING	
25.	Did your child receive colostrum	Yes……1 No……0
26.	When did the child start weaning?	I_____I (months)
27.	How long was the child exclusively breastfed (No water)?	I_____I (months)
28.	Was water included in this time	Yes……1 No……0
29.	Which month did you start adding water?	_____month
30.	Was the water treated	Yes……1 No……0
31.	How was it treated?	
32.	Is the child currently breastfed?	Yes……1 No……0
	MEDICAL HISTORY	
33.	Has the child had any hospitalisations other th immediately after birth?	Yes……1 No……0
34.	Reason for hospitalization	Specify_____.....1 Not Applicable……0
35.	Did the child have diarrhea during the OI doses?	Yes……1 No……0
36.	Do you know the VHN in your area	Yes……1 No……0
37.	What is her name	Don't know……0 Named:(specify)……1
	SOCIOECONOMIC STATUS	
38.	Type of House	No house……0 Pucca……1 Mixed……2 Kutcha……3
39.	Highest Education of Head of Household	
40.	Occupation of the Head of Household	

41.	Income (per month)	
42.	Land Owned (wet)	_____ (acres)
43.	What is your Religion	
44.	What is your Caste	Specify:
	WATER & SANITATION	
45.	What is the main source of drinking water your household?	Piped/Tapincl municipality……1 Borewell……..……2 Dugwell/Spring water…….……3 Water tanker/cart……..…...4 Bottled……...5 Others (specify)_____.....6
46.	Where is the water source located	Inside house/compound…..……1 Outside Compound…….2
47.	How long does it take reach your water source	_____(mins)
48.	Treatment of water given to child	No treatment…… ……..1 Boiling…… …….……2 Filter……,…….3 Boil Filter…….……4 Chemical……5 Others (specify)…… .. ……6
49.	Where do members of your household usua defecate?	Toilet in house/compound…….….1 Community toilet……..2 Open Air/Field…….3
50.	Do you have a toilet in your house?	Yes No
51.	Do you use this toilet	Yes No
	MEDICAL EXAMINATION	
52.	Weight	_____ (kg)
53.	Height/Length	____ (cms)

Annexure 2 - Information Sheet - English

You are being requested to participate in this research. The following information is provided to inform you about this research project. Please read this form carefully and please feel free to ask any questions you may have about the study or the information given below. You will be given an opportunity to ask questions, and your questions will be answered. Also, you will be given a copy of this information sheet.

Your participation in this research study is voluntary.

Purpose of this Research:

Although children are given oral polio vaccine to fight against polio, there are some children who don't develop protection to this virus. Many differences have been noted between those who develop immunity and those who don't. We have come to study risk factors and hope to understand better why some don't develop protection while others do.

If you take part, what will you have to do?

If you agree, we will ask you a few questions regarding your child's immunizations and other questions regarding the birth, breastfeeding and do a quick measurement of the child's height and weight.

Are there any risks involved?

Participation in this study is not expected to present any risk or hazard to you or your child.

Can you withdraw from this study after it starts?

You may remember that your decision to take part is completely up to you. You can decide to stop being part of this study at any time. Dropping out of the study will not pose any disadvantages for you or your baby.

Will you have to pay to participate in this study?

No, there are no costs involved in participating in this study.

Will your personal details be kept confidential?

All information you give us will be kept confidential, and not be shared with the government or any other organization. However, your information may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

Dr. Carol (telephone number: 04162284305 email: caroldevamani@cmcvellore.ac.in)

Annexure 3 - Informed Consent Form - English

Study Title:Risk Factors for lack of seroprotection against type 3 OPV

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my child's participation in the study is voluntary and that I amfree to withdraw at any time, without giving any reason, without medical care or legal rights being affected. [ ]

(iii) I understand that mine or my child's identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).[ ]

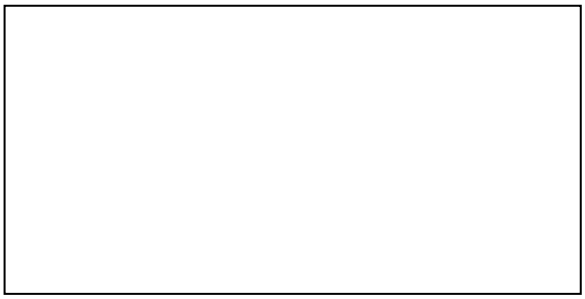
(v) I agree for my child to take part in the above study.[ ]

Signature (or Thumb impression) of the parent/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

Annexure 4 - Information Sheet - Tamil

Title of Research Project: Risk Factors for OPV non-seroconversion

ஆய்வு தலைப்பு: இளம்பிள்ளைவாத சொட்டு மருந்து செயல்படாமல் போவதற்குரிய காரணங்களைக் கண்டறியும் ஆய்வு

தகவல் படிவம்

இந்த ஆய்வில் பங்கேற்க உங்களை அன்புடன் கேட்டுக்கொள்கிறோம். கீழ் கொடுக்கப்பட்டுள்ள தகவல்கள் அனைத்தும் இந்த ஆய்வை குறித்து உங்களுக்கு தெரிவிக்க வழங்கப்படுகிறது. இந்த படிவத்தை கவனமாக படித்து ஏதேனும் கேள்விகள் / சந்தேகங்கள் இருந்தால் கேட்கலாம். உங்களுக்கு கேள்விகள் கேட்க வாய்ப்புகள் அளிக்கப்படும். அதனோடு இந்த படிவத்தின் நகல் உங்களுக்கு வழங்கப்படும். இந்த ஆய்வில் உங்களது பங்கேற்பு முற்றிலும் தன்னிச்சையானது.

a) ஆய்வுக்கான காரணம்:

நோய் வராமல் தடுப்பதற்காக இளம்பிள்ளைவாத கிருமியானது குழந்தைகளுக்கு சொட்டு மருந்தாக கொடுக்கப்பட்டாலும், சில குழந்தைகள் அந்த கிருமிக்கு எதிரான எதிர்ப்பு சக்தியை பெறுவதில்லை. எதிர்ப்பு சக்தியை பெறுபவர்கள் மற்றும் அதனை பெறாதவர்களிடையே பல்வேறு வித்தியாசங்கள் காணப்படுகின்றன. நாங்கள் இதற்கான காரணங்களை ஆராயவும், சிலர் எதிர்ப்பு சக்தியைப் பெறும் போது ஏன் மற்றவர்கள் அதனை பெறுவதில்லை என்பதை புரிந்து கொள்ளவும் விரும்புகிறோம்.

b) நீங்கள் இந்த ஆய்வில் பங்கேற்க விரும்பினால் என்ன செய்ய வேண்டும்?

நீங்கள் சம்மதித்தால், உங்கள் குழந்தைக்கு கொடுக்கப்பட்ட தடுப்பூசிகள் பற்றியும், குழந்தையின் பிறப்பு மற்றும் தாய்ப்பாலூட்டுதல் குறித்தும் சில கேள்விகள் கேட்போம். குழந்தையின் உயரம் மற்றும் எடையையும் விரைவாக எடுப்போம்.

உ) இந்த ஆய்வில் பங்கேற்பதால் உங்கள் குழந்தைக்கு ஏதேனும் பாதிப்பு / ஆபத்து ஏற்படுமா?

இந்த ஆய்வில் பங்கு பெறுவதால் உங்கள் குழந்தைக்கு எந்த பாதிப்பும், ஆபத்தும் ஏற்படாது.

d) இந்த ஆய்வில் பங்கேற்ற பிறகு, நீங்கள் விரும்பவில்லை என்றால் விலகிக்கொள்ளலாமா?

இதில் பங்கேற்பது முற்றிலும் உங்கள் விருப்பத்தைச் சார்ந்தது என்பதை நினைவில் கொள்ளவும். எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து விலகிக் கொள்ள நீங்கள் முடிவெடுக்கலாம். ஆய்வில் இருந்து விலகிக் கொள்வதால் உங்களுக்கோ அல்லது உங்கள் குழந்தைக்கோ எந்த பாதிப்பும் ஏற்படாது.

e) நீங்கள் இந்த ஆய்வில் பங்கேற்க விரும்பினால் ஏதாவது பணம் / கட்டணம் செலுத்து வேண்டுமா?

நீங்கள் இந்த ஆய்வில் பங்கேற்க எந்த பணமும் / கட்டணமும் செலுத்த தேவையில்லை.

f) உங்களுடைய தனிப்பட்ட தகவல்கள் இரகசியமாக வைக்கப்படுமா?

நீங்கள் அளிக்கும் அனைத்து தகவல்களும் இரகசியமாக வைக்கப்படும். அரசாங்கத்திற்கோ அல்லது பிற நிறுவனங்களுக்கோ தெரியப்படுத்தப்பட மாட்டாது.

நீங்கள் ஏதேனும் கேள்வி கேட்க விரும்புகிறீர்களா? இதில் பங்கெடுக்க விரும்புகிறீர்களா? [ஆம் என்றால்]:
மேலும் கேள்விகள் இருந்தால் மருத்துவர் கேரல் அவர்களை 8754689197 என்ற அலைபேசி எண்ணில் தொடர்பு கொள்ளவும்.

Annexure 5 - Informed Consent Form Tamil

Title of Research Project: Factors for lack of seroprotection against type 3 OPV

ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு: Type 3 போலியோவிற்கு எதிராக நோய் எதிர்ப்பு சக்தி இல்லாததற்கான காரணங்கள்

ஆராய்ச்சி எண்:

பங்கேற்பவர் பெயரின் முதல் எழுத்து:

பங்கேற்பவர் பெயர்:

பிறந்த தேதி: வயது

1. நான் இந்த தொகுப்பில் உள்ள ஆராய்ச்சியை பற்றிய விவரங்களை படித்து புரிந்து கொண்டு கேள்விகள் கேட்க வாய்ப்புகள் கிடைத்தன

2. இந்த ஆய்வில் என் குழந்தையின் பங்கேற்பு என் விருப்பத்திற்கு உள்ளானது என்றும் எனக்கு விருப்பமில்லையெனில் எப்பொழுது வேண்டுமானாலும் எந்த காரணமுமின்றி எந்த விதமான மருத்துவ அல்லது சட்டரீதியான உரிமைகளையும் பாதிக்காமல் ஆய்வில் இருந்து என் குழந்தையை வெளியேற்றலாம் என்பதை புரிந்து கொண்டேன்.

3. இந்த ஆய்வில் பங்கேற்பதன் மூலம் என் குழந்தையின் அடையாளமோ அல்லது என்னுடைய அடையாளமோ எந்த பத்திரிக்கைகளிலோ அல்லது வேறு நபர்களுக்கோ வெளிபடுத்தபட மாட்டாது என்று முழுமையாய் புரிந்துக்கொண்டேன்.

4. இந்த ஆய்வின் எந்த தகவல்களையும் மற்றும் முடிவுகளையும் என் அனுமதியின்றி அறிவியல் ஆய்வுக்கு மட்டும் பயன்படுத்தலாம் என்று முழுமையாக ஒப்புக்கொள்கிறேன்.

5. மேற்கண்ட ஆய்வில் என் குழந்தை பங்கேற்கு நான் ஒப்புக்கொள்கிறேன்.

பெற்றோரின் கையெழுத்து (அல்லது பெருவிரல் ரேகை) / சட்டபூர்வமாக ஒப்புக்கொள்ளுதல்

தேதி:

கையெழுத்திட்டவரின் பெயர்: கையெழுத்து:

அல்லது

Title of Research Project: Factors for lack of seroprotection against type 3 OPV

பிரதிநிதி: _____

தேதி: ____/____/_____

கையெழுத்திட்டவரின் பெயர்: _____

ஆராய்ச்சியாளரின் கையொப்பம்: _____

தேதி: ____/____/_____

ஆராய்ச்சியாளரின் பெயர்: _____

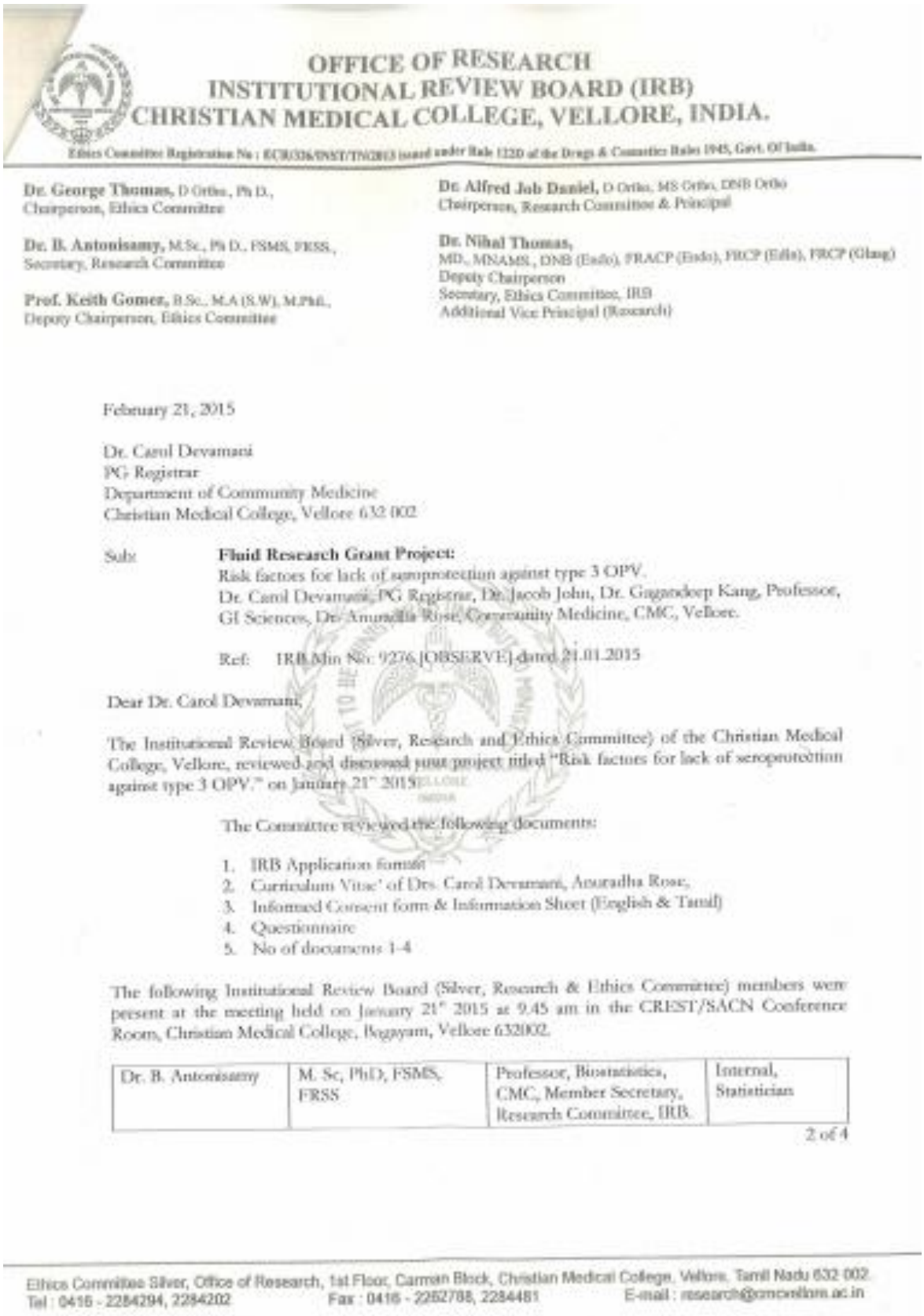
சாட்சியின் கையெழுத்து அல்லது பெருவிரல் ரேகை: _____

தேதி: ____/____/_____

சாட்சியின் பெயர் மற்றும் விலாசம்: _____

_____

Annexure 6 – Institutional Review Board Approval



OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Ethics Committee Registration No : ECR/336/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. Of India.

Dr. George Thomas, D Ortho., Ph D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

February 21, 2015

Dr. Carol Devamani
PG Registrar
Department of Community Medicine
Christian Medical College, Vellore 632 002

Subj: **Fluid Research Grant Project:**
Risk factors for lack of seroprotection against type 3 OPV.
Dr. Carol Devamani, PG Registrar, Dr. Jacob John, Dr. Gagandeep Kang, Professor, GI Sciences, Dr. Anuradha Rose, Community Medicine, CMC, Vellore.

Ref: IRB Min No. 9276 [OBSERVE] dated 21.01.2015

Dear Dr. Carol Devamani,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Risk factors for lack of seroprotection against type 3 OPV." on January 21st 2015.

The Committee reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae of Drs. Carol Devamani, Anuradha Rose,
3. Informed Consent form & Information Sheet (English & Tamil)
4. Questionnaire
5. No of documents 1-4

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on January 21st 2015 at 9.45 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Dr. B. Antonisamy	M. Sc, PhD, FSMS, FRSS	Professor, Biostatistics, CMC., Member Secretary, Research Committee, IRB.	Internal, Statistician

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Ethics Committee Silver, Office of Research, 1st Floor, Carmen Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMC.	Internal, Basic Medical Scientist
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor, Child Health, CMC.	Internal, Clinician
Dr. B. Poonkuzhali	MSC, PhD	Professor, Haematology, CMC.	Internal, Basic Medical Scientist
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, CMC.	Internal, Clinician
Dr. Sathya Subramani	Md. PhD	Professor, Physiology, CMC.	Internal, Clinician
Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMC.	Internal, Clinician
Dr. Molly Jacob	MBBS, MD, PhD	Professor, Biochemistry, CMC	Internal, Clinician
Dr. George Thomas	MBBS, D Ortho, Ph. D	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB.	External, Clinician
Prof. Keith Gomez	BSc, M.A (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Clinical Pharmacology, CMC	Internal, Pharmacologist
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Clinician
Rev. Dr. T. Arul Dhas	M. Sc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMC	Internal, Social Scientist
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Ethics Committee Registration No : ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. Of India.

Dr. George Thomas, D Ortho., Ph D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Shirley David	M. Sc, PhD	Professor, Head of Fundamentals Nursing Department, CMC	Internal, Nurse
Dr. Vinitha Ravindran	PhD (Nursing)	Professor & Addl. Deputy Dean, College of Nursing	Internal, Nurse
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP(En FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 2,150/- INR (Rupees Fourteen Thousand only) will be granted for 6 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin), FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Jacob John, Community Medicine, CMC, Vellore.